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UNITED STATES DISTRICT COURT
NORTERN DISTRICT OF CALIFORNIA

Andrew Williamson on behalf of himself and all others similarly situated,

Plaintiffs,

vs.

Genentech, Inc., and Genentech USA, Inc.,

Defendants.

Case No. 3:19-cv-01840-JSC

HON. JACQUELINE SCOTT CORLEY

FIRST AMENDED CLASS ACTION COMPLAINT

CLASS ACTION

DEMAND FOR JURY TRIAL

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E. Letter from Sarah B. Kotler, Director, Division of Freedom of Information, FDA, to Richard Cornfeld (June 8, 2017)

> *"The federal Medicare program and private health insurers waste nearly $3 billion every year buying cancer medicines that are thrown out because many drug makers distribute the drugs only in vials that hold too much for most patients, a group of cancer researchers has found."*[1]
>
> * * *
>
> "*The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures.... Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use.*"[2]

COMES NOW Plaintiff Andrew Williamson ("Plaintiff"), individually and on behalf of all others similarly situated, and, for his Complaint against Defendants Genentech, Inc., and Genentech USA, Inc. (collectively referred to as "Defendant" or "Genentech") alleges upon personal knowledge as to his own acts and upon information and belief (based on the investigation of counsel), as follows:

INTRODUCTION

1. Plaintiff brings this lawsuit to obtain redress from a practice that needlessly costs patients with cancer and other serious diseases hundreds of millions of dollars a year for costly medicines that cannot be used and instead must be thrown away because of the wasteful way that Genentech packages them.

2. It is a truism that the increasing cost of healthcare in the United States is unsustainable and has a devastating effect on the American economy and on patients and their families in particular.[3]

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[1] Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, quoted in Gardiner Harris, *Waste in Cancer Drugs Costs $3 Billion a Year, a Study Finds*, N.Y. Times, March 1, 2016, at B1 (Ex. C) ("Harris").

[2] Eli Lilly, as stated in Kristin M. Sheffield *et al.*, *Minimization of olaratumab drug waste using real-world data*, 74 Am. J. Health-Syst. Pharm. E270 (2017) ("Sheffield") (Ex. B).

[3] *See* Alex Kacik, *Healthcare costs increasing at unsustainable pace*, Modern Healthcare (6/13/2018), available at https://www.modernhealthcare.com/article/20180613/NEWS/1806199619 (accessed 2/18/2019); J. Sahadi, CNN Business, *Warren Buffet is right. Health care costs are swallowing the economy* (1/30/2018), available at https://money.cnn.com/2018/01/30/news/economy/health-care-costs-eating-the-economy/index.html (accessed 2/18/2019); Niek Stadhouders *et al.*, Effective healthcare cost-containment policies: A systematic review, 123 Health Policy 71 (2019).

A major culprit is the cost of cancer drugs and other drugs.[4] These drugs are a major burden on the economy and on individual patients and their families.

3. The IMS Institute for Healthcare Informatics recently found that "[t]he total cost of oncology therapeutics and supportive care drugs" for cancer worldwide in 2015 was $107 billion, of which 46% (or $49 billion) was spent in the United States.[5]

4. The cost of these drugs for individual patients and their families can be crushing. A recent study found that the average amount spent by patients with colorectal cancer was more than $63,000 during just the first year.[6] Of 13 cancer drugs introduced in 2012, 12 were priced above $100,000 per year, "and the situation has only gotten worse since."[7]

5. The prices of cancer drugs are increasing rapidly. The net price of branded oncology drugs increased by 21.8% from 2010 to 2015.[8] That is nearly three times the increase in overall inflation over that period, as measured by the Consumer Price Index.[9] "[E]ven the cost of existing cancer drugs has been increasing precipitously – well above the rate of inflation and much faster than other aspects of health care."[10]

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[4] Experts in Chronic Myeloid Leukemia, *The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs*, 121 Blood 4439 (2013); Linda A. Johnson, *AARP: Price hikes doubled average drug price over 7* years (2/29/16), available at https://apnews.com/3fabc10146aa4e3285cfbf829d8469c1 (accessed 2/18/2019); Peter Loftus, *Employers Battle Drug Costs*, Wall Street Journal, Dec. 18, 2015, available at http://www.wsj.com/articles/employers-battle-drug-costs-1450488416 (accessed 2/18/2019).

[5] Murray Aitken & Michael Kleinrock, Global oncology trend report. A review of 2015 and outlook to 2020. IMS Institute for Healthcare Informatics, June 2016, at 4.

[6] Christopher T. Chen *et al.*, Medicare Spending for Breast, Prostate, Lung, and Colorectal Cancer Patients in the Year of Diagnosis and Year of Death, Health Serv, Res., pre-publication version available at http://onlinelibrary.wiley.com/doi/10.1111/1475-6773.12745/abstract (accessed 2/18/2019).

[7] Paul Workman *et al., How Much Longer Will We Put Up With $100,000 Cancer drugs*, 168 Cell 579, 579 (2017)

[8] *Id.* at 26, Chart 19.

[9] *See* the United States Bureau of Labor Statistics Inflation Calculator, at https://www.bls.gov/data/inflation_calculator.htm (accessed 2/18/2019), showing an increase in the Consumer Price Index over that period of 7.9%.

[10] Elie Dolgin, *Cancer's cost conundrum*, 555 Nature S26, S26 (2018).

6. In recent years, Defendant's drugs have risen even faster than that. Between May 2017 and February 2019, the Wholesale Acquisition Cost ("WAC"), meaning the manufacturer's list price in the United States, of the four drugs at issue herein increased by 26% (Avastin), 24% (Kadcyla), 30% (Rituxan) and 27% (Xolair). Those increases far outstripped both general inflation and medical care inflation, as measured by the government's Consumer Price Index ("CPI"). During that same time period, the CPI for all urban consumers, all items, increased by only 3%[11] and for medical care increased by only 4%.[12]

7. Cancer drugs have become so expensive that even middle-class patients have been forced to stop taking their medicines – at great risk to their survival – because they cannot afford them.[13] One recent study found that 39% of patients with cancer altered their care by not filling a prescription or taking less medication than prescribed because of treatment-related financial distress.[14] Moreover, those diagnosed with cancer are more than twice as likely to declare bankruptcy than non-cancer patients.[15]

8. The scientific literature refers to the impact on patients of the cost of cancer care as "financial toxicity."[16]

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[11] *See* https://www.bls.gov/data/inflation_calculator.htm (accessed 2/22/2019).

[12] *See* https://fred.stlouisfed.org/series/CPIMEDSL (accessed 2/22/2019).

[13] *See, e.g.*, Joseph Walker, *Patients Struggle with High Drug Prices*, Wall Street Journal, Dec. 31, 2015, available at http://www.wsj.com/articles/patients-struggle-with-high-drug-prices-1451557981 (accessed 2/18/2019).

[14] Ryan D. Nipp *et al., Identifying cancer patients who alter care or lifestyle due to treatment-related financial distress*, 25 Psycho-Oncology 719 (2016).

[15] S. Yousuf *et al., The Utility of Cost Discussions Between Patients with Cancer and Oncologists*, 21 Am. J. Managed Care 607 (2015).

[16] This term was introduced in 2013 in S. Yousuf Zafar *et al., The Financial Toxicity of Cancer Treatment: A Pilot Study Assessing*, 18 Oncologist 381 (2013). According to Google Scholar, this article had been cited by more than 1,600 scientific papers as of February 2019. *See* *https://scholar.google.com/scholar?hl=en&as_sdt=0%2C26&q=%22Financial+Toxicity%22&btnG=* (accessed 2/18/2019). The term "financial toxicity" had appeared in more than 900 scientific papers. *Id.*

9. Another truism is that a reason for runaway healthcare costs is waste, fraud, and abuse. Many people think that those terms simply refer to individual actions by unscrupulous medical providers to perform unnecessary services, overcharge, or provide services that do not meet the standard of care.[17]

10. But that is not a complete understanding of the situation as it pertains to drugs, particularly cancer drugs. In 2016, a paper published in the peer-reviewed journal BMJ (formerly the British Medical Journal) by a group of experts headed by Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes of Memorial Sloan Kettering Cancer Center, revealed another more systemic source of waste. Pharmaceutical companies actually are selling cancer and other expensive drugs in vials that can be used only once but that provide more medicine than is appropriate for most patients, resulting in expensive products simply being thrown away at great cost to patients and their insurers.[18]

11. Dr. Bach's study projected that payments the United States in 2016 for the wasted portions of just 18 cancer drugs, including three manufactured by Genentech, would total $1.8 billion in revenues received by the pharmaceutical companies, with another $1 billion in markups paid to doctors and hospitals. For three Genentech products alone, the total was more than half a billion dollars, not counting wholesale and retail markups. And that is the cost of waste for just one year. But this practice is not new, and these amounts of waste can be multiplied many times over because of what has gone on since this practice began.

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[17] *See* "Addressing Fraud, Waste, and Abuse," at https://www.humana.com/about/legal/disclaimer-and-licensure/fraud-waste-and-abuse (accessed 2/18/2019); Centers for Medicare & Medicaid Services, *Health Care Fraud and Proram Integrity: An Overview for Providers*, available at https://dbhids.org/wp-content/uploads/2015/10/Health-Care-Fraud-and-Program-Integrity-An-Overview-for-Providers.pdf (accessed 2/18/2019); Nicole C. Lallemand, *Reducing Waste in Health Care* (Dec. 13, 2012), available at http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=82 (accessed 2/18/2019).

[18] Peter B. Bach *et al., Overspending driven by oversized single dose vials of cancer drugs*, 352 BMJ 788 (2016) (Ex. A).

12. As the New York Times stated in reporting on the BMJ study: "The federal Medicare program and private health insurers waste nearly $3 billion every year buying cancer medicines that are thrown out because many drug makers distribute the drugs only in vials that hold too much for most patients …."[19]

13. Most patients probably do not know that they are paying large amounts of money for medicines that do not, and cannot, treat them. The New York Times related what happened to Lena Haddad, 53, of Germantown, Maryland:

> On a recent day at Ms. Haddad's doctor's office in Bethesda, Md., a nurse, Patricia Traylor, took a vial of Velcade from a large drug cabinet. She injected a syringeful of saline into the vial and shook it, pushed a needle into the vial and withdrew about half the contents. Then she threw out the vial with the remaining medicine.
>
> "You can't use the remainder for the patient the next time she comes in or use it on another patient, so it has to be discarded as waste," Ms. Traylor said.
>
> Safety standards permit nurses to use drug leftovers in other patients only if used within six hours and only in specialized pharmacies.
>
> Told that she was using only about half of the drug that was purchased, Ms. Haddad said she was shocked.[20]

14. Dr. Bach and his co-authors proposed a simple fix for this serious problem. If each manufacturer, including Genentech, had offered just one additional smaller vial size (meaning a vial with less fill volume) for each of 18 different products, the amount of wasted medicine would have been reduced from $1.8 billion to $400 million per year, an annual savings of $1.4 billion, plus savings of another $600 million in markups to doctors and hospitals that would not have had to be paid. For each of the three Genentech products, the authors proposed one additional vial size that, if implemented, would have reduced the amounts paid for wasted drugs by than $400 million per year, plus associated markups.

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[19] Harris, *supra* (Ex. C).

[20] Harris, *supra*, at 2.

15. Dr. Bach's proposal is feasible. In Europe, drug companies, including Genentech, do just as Dr. Bach recommended. In Europe, Genentech's asthma drug Xolair (annual U.S. Sales: $1.8 billion[21]) is dosed in multiples of 75 mg. But until at least late 2018, Genentech sold Xolair only in 150 mg vials in the United States, leading to large amounts of waste for patients whose prescribed dose was 75, 225 or 375 mg. (In or about late 2018, it introduced 75 mg and 150 mg pre-filled syringes.) But because in Europe Genentech also sells Xolair in 75 mg vials, not one mg of Xolair ever went to waste there.

16. Since the Bach study was published, one company, Eli Lilly, substantially mitigated the problem for one of its cancer drugs. In March 2017, it added a smaller vial size to its existing 500 mg size of olaratumab (Brand Name: Lartruvo) and reported in a peer-reviewed study that this action reduced the amount of wasted product by 87.8%.[22] However, Genentech has not followed that responsible practice, and patients continue to pay hundreds of millions of dollars for medicine that necessarily is wasted.

17. Plaintiff brings this case on his own behalf and on behalf of other end payors (patients and insurers) to recover the amounts they necessarily spent, through no fault of their own, on wasted medicine sold by Genentech.[23] Because absent this Court's intervention, Genentech's practice will undoubtedly continue unchecked for as long as there are cancer drugs. Plaintiff seeks injunctive relief to put a stop to it.

18. Genentech's actions alleged in this complaint violate the California Unfair Competition Law ("UCL"), Cal. Bus. & Prof. Code §§ 17200, *et seq*.

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[21] https://www.fiercepharma.com/special-report/xolair (accessed 2/18/2019).

[22] Kristin M. Sheffield, Julie Kay Beyner, Ian A. Watson, *et al.*, *Minimization of olaratumab drug waste using real-world data*, 74 Am. J. Health-Syst. Pharm. E270 (2017) (Ex. B).

[23] Collectively, these medicines are referred to herein as "subject medicines." They include the medicines manufactured and sold by Defendants as identified in the "Parties" section of the Complaint, as well as any other medicines that Defendants sell in quantities that lead to waste, as identified in discovery.

PARTIES

Plaintiff

19. Plaintiff Andrew Williamson is a resident of Liberty, Missouri, who was treated with Genentech's Rituxan at the University of Kansas Hospital beginning in 2016.

Defendants

20. Genentech, Inc., is a corporation incorporated in Delaware with its principal place of business at 1 DNA Way, South San Francisco, CA 94080. It is a subsidiary of the multinational pharmaceutical giant, Roche. Based in Switzerland, Roche claims to be the world's largest biotech company.[24]

21. Genentech USA, Inc., is a corporation incorporated in Delaware with its principal place of business at 1 DNA Way, South San Francisco, CA 94080. It is a wholly-owned subsidiary of Genentech, Inc.

22. These companies, collectively referred to as "Genentech," manufacture the following drugs that are sold in single-use vials resulting in large amounts of wasted medication.

Avastin

23. Under the brand-name Avastin, Genentech sells the biologic product bevacizumab for treatment of colorectal cancer. FDA approved Avastin in 2004 under the license BLA #125085, and it has been sold in the United States ever since. Genentech classifies Avastin as a BioOncology drug.[25]

24. According to its product label,[26] Avastin is supplied in single-use vials as a solution in two sizes containing either 100 mg or 400 mg. The dosage of Avastin, which is administered by injection, is 5 or 10 mg/kg of body weight, depending on the other drug with which it is administered, for metastatic colorectal cancer. The dosage is 15 mg/kg for treatment of non-squamous non-small cell lung cancer. The dosage is 10 mg/kg for treatment of other cancers.

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[24] *See* https://www.roche.com/about.htm (accessed 2/18/2019).

[25] https://www.gene.com/medical-professionals/medicines (accessed 2/18/2019).

[26] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf (accessed 2/18/2019).

25. According to Dr. Bach's 2016 study, Avastin's sales in the United States in 2016 were expected to be $3.2 billion. That year, it was reported to be the seventh largest-selling drug in the world with $6.8 billion in sales.[27] As of February 2019, its WAC, meaning the manufacturer's list price in the United States, for the larger size was $ 3,732.00 per vial and for the smaller size was $ 933.00 per vial.

Rituxan

26. Under the brand-name Rituxan, Genentech sells the biologic product rituximab for treatment of Non-Hodgkin's Lymphoma ("NHL"), Chronic Lymphocytic Leukemia ("CLL"), and other conditions. FDA approved Rituxan in November 1997, under license numbers BLA # 103705 and BLA # 103737, and it has been sold in the United States ever since. Genentech classifies Rituxan as a BioOncology drug.[28]

27. According to its product label, Genentech supplies Rituxan in single-use vials as solutions in two sizes, 100 mg of Rituxan in 10 mL solution and 500 mg of Rituxan in 50 mL solution; these have the same concentration (10 mg/ml).[29] Its dosage, which is administered by injection, is 375 mg/m^2 of skin area for NHL and 375 mg/m^2 for CLL in the first cycle and 500 mg/m^2 in subsequent cycles.

28. According to Dr. Bach's 2016 study, Rituxan's sales in the United States in 2016 were expected to be $3.85 billion. That year, it was the fourth largest selling drug in the world with $8.6 billion in sales.[30] As of May 2017, the WAC for Rituxan was $ 1,084.06 per 10 mL vial and $ 5,420.28 per 50 mL vial.

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[27] http://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868 (accessed 2/18/2019).

[28] https://www.gene.com/medical-professionals/medicines (accessed 2/18/2019).

[29] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5451lbl.pdf (accessed 2/18/2019).

[30] http://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868 (accessed 2/18/2019).

Kadcyla

29. Under the brand-name Kadcyla, Genentech sells the biologic product ado-trastuzumab entansine for treatment of breast cancer. FDA approved Kadcyla on February 2013 under the license number BLA # 125514, and it has been sold in the United States ever since. Genentech classifies Kadcyla as a BioOncology drug.[31]

30. According to its product label, Kadcyla is supplied in single-use vials as a lyophilized powder in two sizes, 100 mg and 160 mg, both of which must be reconstituted with sterile water.[32] The dosage of Kadcyla, which is administered by injection, is 3.6 mg/kg of body weight.

31. According to Dr. Bach's 2016 study, Kadcyla's sales in the United States in 2016 were expected to be $414 million. As of May 2017, its WAC was $ 5,652.00 per 160 mg vial and $ 3,532.50 per 100 mg vial.

Xolair

32. Under the brand-name Xolair, Genentech co-developed and co-promotes with Novartis Pharmaceuticals Corporation the biologic product omalizumab for treatment of asthma, which Genentech sells in the United States. FDA approved Xolair in June 2003 under license number BLA #103976, and it has been sold in the United States ever since.

33. According to its product label, Xolair is supplied in single-use vials as a lyophilized powder to be reconstituted with water.[33] In the United States, each vial contains 150 mg. Xolair has an FDA-approved 75 mg vial size, which Genentech does not sell in the United States although that size is sold in Europe.[34] Xolair's dosage, which is administered by injection, is between 150 to 375 mg, depending on the patient's serum IgE level and body weight, according to charts on the product label.

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[31] https://www.gene.com/medical-professionals/medicines (accessed 2/18/2019).

[32] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125427s102lbl.pdf (accessed 2/18/2019).

[33] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf (accessed 2/18/2019).

[34] Bach *et al.* (2016) at p. 2 or 7; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf (accessed 2/18/2019).

34. In or about late 2018, Genentech introduced 75 mg and 150 mg prefilled syringes of Xolair in the United States. It did not introduce a 75 mg vial.[35]

35. Genentech's parent, Roche, reported that Xolair's sales in the United States in 2017 were 1,742 million Swiss francs,[36] or approximately $1.8 billion. As of May 2017, the WAC for Xolair, was $1,022.49 per vial in the United States.

JURISDICTION AND VENUE

36. This Court has jurisdiction over this action pursuant to the Class Action Fairness Act (28 U.S.C. § 1332(d)). The aggregated claims of the individual class members exceed $5,000,000, exclusive of interest and costs, at least one class member is of diverse citizenship from one defendant, and there are more than 100 class members.

37. This Court has personal jurisdiction over Defendants because they conduct business in California and have sufficient minimum contacts with California.

38. Venue is proper in this District under 28 U.S.C. § 1391(b) because a substantial part of the events or omissions giving rise to the claims occurred and/or emanated from this District, where Genentech has its principal place of business, and because Genentech has caused harm to class members residing in this District.

FACTUAL ALLEGATIONS REGARDING GENENTECH'S LIABILITY

The Bach Article

39. In early 2016, the peer-reviewed journal *The BMJ* (formerly the British Medical Journal) published a scientific paper entitled "*Overspending driven by oversized single dose vials of cancer drugs,*" which presented the results from a study by Peter Bach and colleagues at Memorial Sloan Kettering Cancer Center and the University of Chicago on wasteful healthcare spending.[37] *The BMJ* is

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[35] https://www.pharma.us.novartis.com/news/media-releases/novartis-announces-fda-approval-xolair-omalizumab-prefilled-syringe-formulation (accessed 2/18/2019).

[36] https://www.roche.com/dam/jcr:8476522e-ecb4-4c65-b91d-4a8301ccb14b/en/180201_IR_FY_release_en.pdf accessed 2/18/2019).

[37] Peter B. Bach *et al.*, *Overspending driven by oversized single dose vials of cancer drugs*, 352 BMJ 788 (2016) (Ex. A) ("the Bach study" or "Bach *et al.* (2016)").

one of the world's most prestigious scientific journals. In 2016, it ranked fourth in the world among general medical journals in "impact factor," a widely recognized measure of a journal's importance in its scientific field.[38]

40. Bach *et al.* (2016) reported on "the waste that can be created when expensive infused drugs are packed containing quantities larger than the amount needed." *Id.* at 1. As the authors stated:

> These drugs must be either administered or discarded once open, and because patients' body sizes are unlikely to match the amount of drug included in the vial, there is nearly always some left over. The leftover drug still has to be paid for, even when discarded, making it possible for drug companies to artificially increase the amount of drug they sell per treated patient by increasing the amount in each single dose vial relative to the typically required dose.

41. In their paper, Dr. Bach and his colleagues studied 20 cancer drugs, as well as two non-cancer drugs, including four drugs sold by Genentech: Avastin (generic name: bevacizuma); Rituxan (generic name: rituximab); Kadcyla (generic name: Ado-trastuzumab emtansine); and Xolair (generic name: omalizumab). Because these vials cannot be safely reused, any leftover amount must be discarded except in unusual circumstances. As a result, large amounts are not used and must be thrown away.

42. The authors stated: "Regularly and systematically discarding expensive drugs is antithetical to efforts to reduce spending on healthcare services that provide no value." Bach *et al.* (2016) at 2.

43. Patients and their third-party payors pay substantial sums for the unused amounts in the vials.

44. According to Dr. Bach, as quoted in the *Washington Post*, patients and their third-party payors are "literally paying for drugs that go in the trash.... [Drug companies] are finding a way to charge patients and insurers for drugs that they don't even take."[39]

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[38] *See* http://www.bmj.com/about-bmj (accessed 2/18/2019).

[39] Laurie McGinley, "Americans are wasting $3 billion a year on discarded cancer drugs," March 1, 2016. (Ex. D.)

45. In their study, Bach and his colleagues "calculated the total amount of leftover drug and resulting 2016 US revenues for each drug ...." Bach *et al.* (2016) at 1. Their estimate was that for 20 cancer drugs manufacturers received, in the aggregate, $1.8 billion in annual revenues from discarded drugs. *Id.* at 1-2. Because of wholesale and retail markups, end payors paid much more than that for wasted drugs, in excess of $1 billion more. *Id.* at 2. Thus, the total amount that end payors paid for wasted amounts of these 20 drugs approached $3 billion in 2016 alone.

46. The authors made a simple and effective proposal for reducing the amount of waste: for each drug product, the seller would introduce one additional and smaller vial size. Their proposal would reduce the aggregate manufacturers' revenues for these drugs from $1.8 billion to $400 million per year and would save end payors approximately $2 billion a year. *Id.* at 2.

47. Bach *et al.* used the term "vial size" to refer not to the size of the vial or container, but to the amount of the drug in the vial (*i.e.*, the fill volume). For example, they referred to a "75 mg vial size" of one drug and "100 mg vial sizes" of another. *Id.* at 2, 5. Their reference to "vial size" is therefore not to the size of the container but to the amount of drug in the container. The containers of these drugs do not weigh 75 or 100 mg; the drug in the containers do. Similarly, in this Amended Complaint, Plaintiff uses the term "vial size" to refer to the amount of drug in the vial.

Other Investigators Agree with Bach

48. Other investigators agree on the financial impact of this wasteful practice. In 2017, the National Academy of Science published a Consensus Study Report entitled *Making Medicines Affordable: A National Imperative*.[40] Members of the committee that authored this work included academics, government officials, employees of insurers such as United Health and Blue Cross Blue Shield, and nonprofit health study groups such as the Henry J. Kaiser Family Foundation. The committee also included a former Chief Medical Officer of Merck & Co., Inc., and a former President and CEO of Genzyme Corporation, both manufactures of anti-cancer drugs.[41]

[40] National Academies of Sciences, Engineering, and Medicine, *Making medicines affordable: A national imperative.* Washington, DC (2017) (*Making Medicines Affordable*).

[41] *Making Medicines Affordable* at vii-viii.

49. Chapter 3 of *Making Medicines Affordable* is entitled "Factors Influencing Affordability."[42] One of those factors is "Waste and Cost Due to Unused Drugs in the Supply Chain." Citing Bach *et al.* (2016), the authors stated:

> Every year drugs worth billions of dollars that have been purchased by health care organizations (e.g., retail pharmacies, hospitals, nursing homes) and patients are discarded. Some of this waste in the system could be eliminated by changing the way drugs are packaged and labeled. For example, vials of infused drugs are often available only in a single dose size that is sufficient to treat a physically large patient. As a result, the remaining drug must be discarded when a smaller patient is treated. Because 18 of the top 20 infused cancer drugs are sold in just one or two vial sizes, 10 percent of the purchased drug amount is discarded on average (Bach et al., 2016). Manufacturers propose dose sizes for marketing, and the FDA only reviews the request for safety considerations [citation omitted].[43]

50. Similarly, in 2017, the Organization for Economic Co-operation and Development ("OECD"), an organization of 35 countries (including the United States) devoted to "foster[ing] prosperity and fight[ing] poverty,"[44] published a report entitled *Tackling Wasteful Spending on Health.*[45] In a section entitled "Discard of unused pharmaceuticals and other medical supplies," the Report cited Bach *et al.* (2016) for the following:

> Discard of pharmaceuticals used in hospitals often occurs due to the too-large package size of single-dose drugs. This is particularly true for drugs whose dosage is based on a patient's body weight or size and come in single-dose packages. Such packaging means that these drugs must be either administered or discarded once open. When packaging is such that a patient's body size is unlikely to match the amount of drug in a single dose, some is nearly always left over. For example, a recent study estimates that unused leftover infused single-vial cancer drugs cost an additional USD 2 billion annually in the United States (Bach et al., 2016).[46]

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[42] *Making Medicines Affordable* at 73-124.

[43] *Making Medicines Affordable* at 99-100.

[44] *See* http://www.oecd.org/about/ (accessed 2/18/2019).

[45] OECD, *Tackling Wasteful Spending on Health* (2017) ("Tackling Wasteful Spending").

[46] Tackling Wasteful Spending at 163.

51. In an editorial published in the peer-reviewed *Journal of Cancer* in September 2017, Dr. John Valgus of the University of North Carolina Medical Center, stated: "How significant is this problem of wasted cancer drugs? ... When formalized evaluations looking at the impact of cancer drug wastage are completed, the results are unanimous: the impact is significant."[47]

52. Writing in the peer-reviewed JAMA Oncology in early 2008, Daniel A. Goldstein of the Winship Cancer Institute at Emory University and his co-author stated: "Drug wastage is of economic importance. Of note, Bach et al recently estimated that over-sized vials for cancer drugs may lead to $3 billion of overspending each year. Real-world data from Canada have reinforced these claims, demonstrating the problems and potential solutions for drug wastage owing to oversized vials."[48]

53. At least one manufacturer of cancer drugs agrees with these principles and their importance. In a peer-reviewed 2017 paper, authors from Eli Lilly and Company stated: "The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures.... Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use."[49]

54. Two British researchers, writing in the journal *Applied Health Economics and Health Policy* in December 2018, could have been talking about Genentech when they stated that "where the larger vial is perfectly divisible by the smaller vial, i.e. one is a multiple of the other, wastage is higher. This is unsurprising, as vial sizes that are not divisible can create more combinations with no wastage.... Despite this seemingly obvious finding, many novel pharmaceuticals are available only with perfectly divisible vial sizes."[50] Those pharmaceuticals include Genentech's Avastin (400 mg and 100 mg) and Rituxan (500 mg and 100 mg).

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[47] John M.Valgus, Cancer Drug Wastage: *The Hidden Cost in Value-Based Cancer Care Delivery*, 123 Cancer 3445, 3445 (2017).

[48] Daniel A. Goldstein & Abigail Hirsch, *A Policy That Encourages Wastage of Expensive Medications—The JW Modifier*, 4 JAMA Oncol. 155, 155 (2018) (footnotes omitted).

[49] Sheffield *et al.* at e269-e270 (2017).

[50] Anthony J. Hartswell & Joshua K. Porter, Reducing Drug Wastage in Pharmaceuticals Dosed by Weight or Body Surface Areas by Optimising Vial Sizes, Appl Health Econ Health Policy (2018).

Amounts that Class Members Needlessly Spend on Unusable Mediations Are Substantial.

55. The amount spent on wasted drugs for just one patient can total many thousands of dollars a year for Genentech's drugs.

Avastin

56. Avastin is sold in vials containing either 100 mg or 400 mg. The initial dosage of Avastin for patients with lung cancer at the outset of treatment is 15 milligrams per kilogram of body weight, or 1,218 mg for the average male patient and 1,013.1 for the average female patient (average weight: 81.20 kg for men and 67.54 kg for women). [51] To meet that dose, the average male patient must receive three 400 mg vials and one 100 mg vial (1,300 mg altogether), with 82 mg, or 82% of the 100 mg vial, being unused and thrown away. The average female patient would receive two 400 mg vials and three 100 mg vials (1,100 mg in total), with 86.1 mg, or 86.1% of the last 100 mg vial, being unused and going to waste.

57. The cost of those wasted amounts can run into many thousands of dollars per patient. The WAC – the published list price charged by the manufacturer – of a 100 mg vial of Avastin in February 2019 was $ 933.00 . But because 82 mg of the drug had to be discarded, Genentech received $756.06 for wasted drug from just that one treatment. Similarly, Genentech received $803.31 for wasted drug for the average female patient's treatment in May 2017.

58. Genentech's recommended course calls for the treatment to be repeated every three weeks.[52] Thus, for the average patient receiving Avastin for lung cancer, Genentech reaps $12,096.96 and $12,852.96, for males and females, respectively, in annual revenues for Avastin that must be thrown away.

59. Those amounts are just what the manufacturer receives. Patients and insurers must pay much more because of wholesale and retail mark-ups. *See* Bach *et al.* (2016) at 2 ("We have focused on how much money companies earn in terms of revenues from leftover drug, not how much payers

[51] Sheffield *et al.*, (2017) at Table 3 (Ex. B).

[52] *See* Avastin label at § 2.2, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125085s225lbl.pdf (accessed 2/18/2019).

and patients are spending on them, which is a larger number due to the fact that distributing intermediaries and treating doctors and hospitals mark-up drugs when they bill for them.").

60. In Table 1, Bach *et al.* (2016) list the manufacturers' expected 2016 revenue from wasted drug. For Avastin, that amount comes to $284.49 million per year.

Rituxan

61. Rituxan is sold in 100 and 500 mg vials. The dose for Non-Hodgkin's Lymphoma is 375 mg/m^2, or 637.5 mg for the typical patient, according to data presented by Bach *et al.* on BMJ's website.[53] The typical patient must be administered one 500 mg vial and two 100 mg vials, with 62.5 mg in the last vial going to waste.

62. The WAC for the 100 mg vial of Rituxan in February 2019 was $1,084.06. Thus, Genentech reaped $677.54 from the wasted portion of 62.5 mg with that one treatment. Because the recommended course of treatment includes four, eight, or twelve doses over several weeks,[54] Genentech's revenue from the sale of unneeded drug for treatment of a typical patient is $2,710.16, $5,420.32, or $8,130.48.

63. According to Bach *et al.* (2016), Genentech receives $253.9 million in annual revenue from the wasted portions of all the Rituxan it sells in the United States.

Kadcyla

64. Genentech's Kadcyla is sold in 100 mg and 160 mg vials for breast cancer with a dose of 3.6 mg/kg. According to Sheffield *et al.* (2017), the average patient with breast cancer weighs 76.31 kg. That means that the average patient receives a dose of 274.716 mg, which requires three 100 mg vials, with 25.284 mg left over from the last vial.

65. The WAC in May 2017 for the 100 mg vial was $3,532.50; thus, Genentech received $893.16 per dose for the leftover amount of 25.284 mg from one treatment of a typical patient with Kadcyla. Genentech's total revenue for unneeded drug per typical patient is much more than that

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[53] BMJ 2016;352:i788, http://www.bmj.com/content/352/bmj.i788 (accessed 2/18/2019).

[54] *See* Rituxan label at § 2.2, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103705s5432lbl.pdf (accessed 2/18/2019).

because Kadcyla is administered "every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity."[55]

66. Bach *et al.* (2016) estimate that Genentech received $23.7 million per year for the total discarded amount of Kadcyla.

Xolair

67. In the United States, until at least late 2018, Genentech's asthma drug Xolair was sold only in 150 mg vials, even though FDA had approved the product in 75 mg vials. For many patients, the Xolair dose is exactly 75 mg, 225 mg, or 375 mg, as shown in the following table, with the result that, for those patients, half of one vial invariably had to be discarded. [56]

Patients 12 and older		
Dose (mg)	**Weight (kg)**	**Pre-Treatment Serum IgE (IU/mL)**
225	>60-70	>200-300
225	>60-70	>300-400
225	>70-90	>200-300
225	>90-150	>100-200
375	30-60	>600-700
375	>60-70	>500-600
375	>70-90	>300-400

[55] *See* Kadcyla label at § 2.1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125427s096lbl.pdf (accessed 2/18/2019).

[56] *See* Xolair's label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. (accessed 2/18/2019).

Patients from 6 to younger than 12		
Dose (mg)	**Weight (kg)**	**Pre-Treatment Serum IgE (IU/mL)**
75	20-40	30-100
225	20-25	>300-500
225	20-25	>700-1100
225	>25-30	>300-400
225	>25-30	>600-900
225	>30-40	>400-700
225	>40-50	>300-500
225	>50-60	>300-400
225	>60-70	>200-400
225	>70-90	>200-300
225	>90-125	>100-200
375	>25-30	>1200-1300
375	>30-40	>900-1100
375	>40-50	>700-900
375	>50-60	>600-700
375	>60-70	>500-600
375	>70-90	>400-500
375	>125-150	>200-300

68. Patients in each of the above categories required 75 mg from one of their 150 mg vials, with 75 mg, or 50%, of that vial, being unused and discarded. Because the WAC for Xolair in May 2017 was $1,022.49, the manufacturer received $511.25 for the wasted portion of that one treatment.

69. The course of treatment for Xolair includes a dose every two or four weeks. Thus, the wasted amount for each treatment can be multiplied by 26 or by 13 to determine the amount the manufacturer received every year from each such patient or insurer for medicine that had to be thrown away ($13,292.37 or $6,646.19).

How Genentech Could Have Easily Reduced the Amount of Waste

70. Genentech could have substantially reduced the amount of waste by adding just one additional vial size per product. Bach *et al.* (2016) showed how to do it.

71. For example, if, as Bach *et al.* recommended, Genentech had added a 20 mg size to the existing 400 mg and 100 mg vials of its colorectal drug Avastin, the average male patient – who, as shown above, requires 1,218 mg – could have been treated with three 400 mg vials and one 20 mg vial (instead of a 100 mg vial to go with the three 400 mg vials). That would have reduced the amount of

wasted medicine from 82 mg to only 2 mg, a reduction of 97.5%, while not increasing the number of vials per treatment. Similarly, the average female patient – who, as shown above, requires 1,013.1 mg – could have been treated with two 400 mg vials, two 100 mg vials and one 20 mg vial (replacing one 100 mg vial). That would have reduced the amount of wasted drug from 86.1 mg to 6.9 mg, a reduction of 92.0%. Again, it would not have increased the number of vials per treatment.

72. Bach *et al.* (2016) proposed one additional size for each of 18 cancer products including the three Genentech cancer products at issue in this case. In each instance, if Genentech had added that smaller size, there would have been a large reduction in the amount wasted. The table below shows the reduction in waste for the average or typical patient treated with Genentech's products (all quantities are mg except as noted):

Drug	Existing vial(s)	Added vial	Typical/ average dose	Existing wasted drug	Revised wasted drug	Pctg. reduction
Avastin	400, 100	20	1,218 (m) 1,013.1 (f)	82 (male) 86.1 (female)	2 (male) 7.9 (female)	98% 91%
Kadcyla	160, 100	20	274.716	25.284	5.284	79%
Rituxan	500. 100	40	637.5	62.5	2.5	96%

73. The number of vials needed to provide the typical or average dose would not have been increased if Genentech had offered the added vial that Bach *et al.* (2016) recommended. As noted above, the average male and female patient would have needed four and five vials of Avastin, respectively, the same as with the existing vials. Similarly, the average or typical patient would have needed three vials of Kadcyla or three vials of Rituxan, the same as with the existing vials.

74. In the case of Xolair, if Genentech had introduced a 75 mg vial, it would not have increased the number of vials needed per treatment. Instead, it would have meant replacing one 150 mg vial with a 75 mg vial for patients who had Xolair go to waste. In each instance, that was 75 mg wasted out of a 150 mg vial.

75. Bach *et al.* (2016) showed the aggregate financial savings that would have resulted when all patients are considered. The following table, adapted from Bach *et al.*'s Table 3, shows those savings for Genentech's cancer drugs. The last two columns show the annual dollar value of the waste from existing vials and the lesser amount that would result from adding one more vial size (both in

millions of dollars):

Bach *et al.*'s proposed additional vial sizes to reduce the amount of waste on leftover drug

Name	Currently available vial sizes (mg)	Proposed Additional vial size	Estimated waste in 2016 ($million)	
			With existing vials	With additional vial
Avastin	400, 100	20	$284	$60
Kadcyla	160, 100	20	$24	$12
Rituxan	500, 100	40	$254	$53
Total	—	—	$562	$125

76. The sums in the last two columns indicate that Genentech's annual revenues from wasted subject medicines totaled $562 million with its existing vial sizes but would have been reduced to $125 million, a savings of $437 million, with the addition of one smaller vial for each drug. These savings are understated because they do not account for doctor and hospital markups on these drugs. (The mark-ups would have been calculated on lower amounts for the smaller vials.) When lower mark-ups are included, the total savings would have been even larger.

77. Rather than limiting Xolair to 150 mg vials, Genentech could have eliminated *all* waste of Xolair by marketing the already approved 75 mg vial size as it does in Europe or by doing as it did in or about late 2018 in marketing 75 mg prefilled syringes of Xolair in the United States.

Two Manufacturers That Minimize Waste

78. Minimizing waste is feasible. Two other manufacturers have minimized waste by making small vial sizes available.

Treanda

79. Cephalon, Inc., a subsidiary of Teva Pharmaceuticals, Ltd., sells its leukemia drug Treanda in four different single-use vial sizes. Two vial sizes contain a lyophilized powder, either 100 mg or 25 mg, that are to be reconstituted with sterile water. Two contain solutions with either 45 or 180 mg of the drug.[57]

[57] *See* October 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022249s022lbl.pdf (accessed 2/18/2019).

80. When it was introduced in 2008, Treanda was sold in only one size, 100 mg.[58] The following year Cephalon added the 25 mg size[59] and subsequently the 45 mg and 180 mg sizes.

81. As Bach *et al.* (2016) report, this array of sizes enables medical providers to administer the drug without significant waste. Treanda's dosage is 100 mg/m^2. According to data presented by Bach *et al.* on BMJ's website,[60] that works out to a dose of 170 mg for a typical patient. As Bach *et al.* (2016) report, the medical provider can combine one vial each of the 100, 45, and 25 mg sizes to provide the exact dose for the typical patient with no waste (as well as either the exact dose or nearly the exact dose even for atypical patients). As a result, Bach *et al*. (2016) estimate that an average of only 1% of Treanda is wasted.

82. There is no reason why Genentch could not have done (and could not now do for Avastin, Rituxan, and Kadcyla) the same thing for its four products at issue in this lawsuit by adding smaller sizes to reduce or eliminate waste.

Lartruvo

83. Another example of a company that responsibly sized a product to reduce waste is Eli Lilly, which introduced its Lartruvo biologic product (generic name: olaratumab) to treat soft tissue sarcoma and other cancers. FDA licensed Lartruvo in October 2016 pursuant to the license BLA # 761038.

84. As originally licensed, Lartruvo came in only 500 mg vials. However, as explained below, in March 2017, Eli Lilly added a smaller size vial of 190 mg.

85. In a peer-reviewed publication in the American Journal of Health-System Pharmacists, Eli Lilly's scientists reported on the study that led it to introduce that smaller size.[61] This journal "is

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[58] *See* the original Treanda label at https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022249lbl.pdf (accessed 2/18/2019).

[59] *See* April 2009 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022249s001lbl.pdf (accessed 2/18/2019).

[60] BMJ 2016;352:i788, http://www.bmj.com/content/352/bmj.i788 (accessed 2/18/2019).

[61] Sheffield, *et al.*, (2017) (Ex. B).

the official publication of the American Society of Health-System Pharmacists" and "is the most widely recognized and respected clinical pharmacy journal in the world."[62]

86. In the introduction to their article, these Eli Lilly scientists explained the reason for their study: "The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures.... Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use." Sheffield *et al.* at e269-e270 (2017).

87. According to these Eli Lilly scientists, "available vial sizes often are not well suited to cost-efficient administration of the drug dosages possible across the distributions of patient weight and BSA [body surface area]." *Id.* at e270. The authors made clear where the solution to this problem lies: "Manufacturers can help reduce waste by producing appropriate and multiple vial sizes based on the distribution of body sizes across the targeted patient population." *Id.*

88. To advance that process, the Eli Lilly scientists conducted a study to determine the weight and BSA data of patients with various forms of cancer. Eli Lilly then used the study results to determine the "optimal volume for a planned new olaratumab [brand-name: Lartruvo] vial size and quantify the reduction in drug waste with the addition of the new vial size." *Id.*

89. Based on the results of this study, Eli Lilly added a smaller, 190 mg-size vial in March 2017 to its existing 500 mg vial.[63] The addition of the smaller vial reduced waste by 87.6%. *Id.* at e269.

90. The authors indicated that Eli Lilly carefully selected a new vial size that would limit the number of vials needed per treatment to six or fewer. They stated:

> The objectives of waste minimization and vial minimization cannot be simultaneously optimized. At the extreme, producing very small vial sizes would allow for almost any dose with minimal waste. However, preparation would become unduly burdensome for the pharmacy to handle numerous vials. In addition, producing very small vial sizes may increase

[62] http://www.ajhp.org/content/mission-and-vision (accessed 2/18/2019).

[63] *See* http://www.njsom.org/aws/NJSOM/asset_manager/get_file/152920 (accessed 2/18/2019) for introduction date.

> the potential for medication errors and microbial contamination. Therefore, to control pharmacy handling, we imposed a limit of no more than 6 vials to be opened for any given patient.

Id. at e275-e276 (footnote omitted). As noted above, if Genentech had followed Bach *et al.*'s recommendation, it would not have had to increase the number of vials per treatment for the average or typical patient.

91. The benefits of the 190 mg vial for Lartruvo can be seen by looking at patients of average weight with soft tissue sarcoma, which this study found to be 85.27 kg for male patients and 72.89 for female patients. *Id.* at e274, Table 3. Lartruvo's dose is 15 mg/kg. *Id.* at e271. Thus, the total dose for a male soft tissue sarcoma patient of average weight is 1,279.05 mg. If just 500 mg vials were available, that would require three vials, leaving 220.95 mg left over. However, a patient could be administered two 500 mg and two 190 mg vials for a total of 1,380 mg, with only 100.95 mg left over. The difference in price is considerable. In May 2017, the WAC for a 500 mg vial of Lartruvo was $2,360 or $7,080 for three vials. But the WAC for a 190 mg vial was only $896.80 per vial or $6,513.60 for two 500 mg vials and two 190 mg vials. With administration of two 500 mg vials and two 190 mg vials, there would be four vials but a savings of $566.40.

92. Female patients realized similar savings from the smaller vial of Lartruvo. The dose for soft tissue sarcoma in a female patient of average weight is 1,093.35 mg (72.89 kg times 15 mg/kg). With only 500 mg vials, that would require three vials, leaving 406.65 mg left over. But a female patient would get the correct dose from six 190 mg vials, providing a total of 1,140 mg, with only 46.65 left over. Again, the price difference is substantial. The WAC for three 500 mg vials, as shown above, is $7,080; for six 190 mg vials it is $5,380.80, representing a savings of $1,699.20.

93. Sheffield *et al.* (2017) states that one of its "key points" is that "[m]anufacturers can help reduce drug waste by producing multiple vial sizes based on weight and BSA distributions across the targeted patient population in actual clinical practice." *Id.* at e270. Yet, two years after the scientific literature described how Eli Lilly had altered its vial sizes and the consequences of doing so, Genentech has not followed Eli Lilly's example.

Genentech Offered a Smaller Size of Xolair in Europe, but Not in the United States.

94. Bach *et al.* (2016) report that many manufacturers are already doing in Europe, but not in the United States, what these authors and Eli Lilly recommend: selling smaller vial sizes to save money for patients and insurers. Dr. Leonard Saltz, a co-author of the Bach study, told the New York Times: "You have these incredibly expensive drugs, and you can only buy them in bulk. What's really interesting is that they're selling these drugs in smaller vials in Europe …."[64]

95. One example of this Europe-United States discrepancy was Genentech's asthma treatment Xolair. Xolair is sold in 75 mg vials in Europe,[65] but until in or about late 2018 only in 150 mg vials in the United States. Xolair is dosed in 75 mg increments (*i.e.*, 75 mg, 150 mg, 225 mg, etc.), depending on the patient's age, weight, and serum IgE level. This means that no amount of Xolair *ever* systematically goes to waste in Europe. But until at least late 2018 for all patients whose dose was not evenly divisible by 150, half a vial, or 75 mg, was wasted with every treatment in the United States.

96. There is no legitimate reason why, before late 2018, Genentech could not have given U.S. patients the benefit of the smaller vial sizes that it gave to patients in Europe.

FACTS RELATED TO PLAINTIFF'S TREATMENT WITH GENENTECH'S DRUGS

97. Beginning in January 2016, Plaintiff was treated with Rituxan for Follicular Lymphoma at the University of Kansas Hospital in Kansas City, Kansas**.**

98. Between January 28, 2016 and June 16, 2016, Plaintiff was treated six times with Rituxan, each time with a dose of 772.5 mg. On each of these occasions, the hospital used either eight 100 mg vials or one 500 mg vial and three 100 mg vials; on each occasion, the total charges were $34,189.33 per treatment.

99. From September 15, 2016 until August 24, 2017, Plaintiff was given a second course of treatment, each time with a dose of 780 mg of Rituxan. On each of these occasions, the hospital used

[64] Harris, *supra*, at 2.

[65] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf (accessed 2/18/2019).

one 500 mg vial and three 100 mg vials. On the first four treatments during this course, the charges were $37,464.99 per treatment. On the last treatment during this course, the charges were $43,230.99.

100. Beginning on November 16, 2017, Plaintiff was given a third course, with treatments of 800 mg. On November 16, 2017 and March 1, 2018, the hospital used one 500 mg vial and three 100 mg vials, for which the charges were $43,230.99. Notably, this was the same charge that the hospital imposed for the treatment on August 24, 2017, even though the dose was 780 mg on August 24, 2017, and 800 mg for the later treatments.

101. Because Genentech supplies Rituxan in only 500 mg and 100 mg single-use vials, Plaintiff's medical provider was forced to use vials totaling 800 mg for each treatment, even when the prescribed dosage was less than 800 mg. Thus, 27.5 mg had to be discarded for each of the treatments with a dose of 772.5 mg and 20 mg had to be discarded for each of the treatments with a dose of 780 mg. The charges for the unused portions of Rituxan totaled $11,878.82.

102. If Genentech had added a 40 mg vial of Rituxan, Plaintiff's doctors could have used one 500 mg vial, two 100 mg vials, and two 40 mg vials to reduce the amount of unused drug to 7.5 mg and 0 mg per treatment for the first two courses respectively. That vial configuration would have meant that Plaintiff's treatment could have been accomplished with five vials, fewer vials than Eli Lilly's self-imposed limit of six vials. That vial configuration would have reduced the charges for unused Rituxan to $1,923.25, representing a savings of $9,955.67.

103. For each of these treatments, some or all of the hospital charges were paid by Mr. Williamson's insurer. For the treatment of March 2, 2017, Mr. Williamson paid $231.15 out of his own pocket.

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104. The following table shows information from Mr. Williamson's hospital records for each of these treatments.

Date	Dose	Total in vials (mg)	Hospital charges	$/mg in vial	Amt unused (mg)	Chg for unused portion	Amt unused w/40 mg vial	Chg for unused w/40 mg vial	Savings
1/28/2016	772.5	800	$34,189.32	$ 42.74	27.5	$1,175.26	7.5	$320.52	$854.73
2/25/2016	772.5	800	$34,189.32	$ 42.74	27.5	$1,175.26	7.5	$320.52	$854.73
3/24/2016	772.5	800	$34,189.32	$ 42.74	27.5	$1,175.26	7.5	$320.52	$854.73
4/21/2016	772.5	800	$34,189.32	$ 42.74	27.5	$1,175.26	7.5	$320.52	$854.73
5/19/2016	772.5	800	$34,189.32	$ 42.74	27.5	$1,175.26	7.5	$320.52	$854.73
6/16/2016	772.5	800	$34,189.32	$ 42.74	27.5	$1,175.26	7.5	$320.52	$854.73
9/15/2016	780	800	$37,464.99	$46.83	20	$936.62	0	$0	$936.62
12/8/2016	780	800	$37,464.99	$46.83	20	$936.62	0	$0	$936.62
3/2/2017	780	800	$37,464.99	$46.83	20	$936.62	0	$0	$936.62
5/25/2017	780	800	$37,464.99	$46.83	20	$936.62	0	$0	$936.62
8/24/2017	780	800	$43,230.99	$54.04	20	$1,080.77	0	$0	$1,080.77
11/16/2017	800	800	$43,230.98	$54.04	0	$ 0	0	$0	$0
3/1/2018	800	800	$43,230.99	$54.04	0	$ 0	0	$0	$0
Total	**10,135**	**$10,400**	**$484,688.88**	**N/A**	**265**	**$11,878.82**	45	$1,923.15	**$9,955.67**

GENENTECH'S SCHEME ORIGINATED AND IS DIRECTED FROM CALIFORNIA

105. On information and belief, Genentech made the decisions and took the actions that violated the UCL in California. This belief is based on the following:

106. California is the center of Genentech's business operations. According to Genentech's website, www.gene.com, Genentech maintains three facilities in California: its headquarters in South San Francisco; a research, manufacturing, and business center in Oceanside; and a manufacturing plant in Vacaville.

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107. Genentech's campus in South San Francisco includes "multiple buildings that house an advanced research center, manufacturing operations and various business functions. The South San Francisco campus continues to serve as Genentech's corporate headquarters and is also the headquarters for Roche's pharmaceutical operations in the United States."[66] Roche is Genentech's parent.

108. The current labels of each of the subject medicines indicate that they were manufactured by Genentech, with an address in South San Francisco:

A. Avastin:

Avastin® (bevacizumab)
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990[67]

B. Kadcyla:

KADCYLA® [ado-trastuzumab emtansine]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No: 1048[68]

C. Rituxan:

RITUXAN® [rituximab]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No: 1048[69]

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[66] https://www.gene.com/contact-us/visit-us/s-san-francisco (accessed 2/18/2019).

[67] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf (accessed 2/18/2019).

[68] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125427s102lbl.pdf (accessed 2/18/2019).

[69] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5451lbl.pdf (accessed 2/18/2019).

D. Xolair:

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No: 1048[70]

109. Most of Genentech's employees are located in California. On its website, www.gene.com, Genentech instructs readers to "Get to know us better. Check us out on ... LinkedIn" and links to Genentech's page on LinkedIn.[71] Genentech's page in turn links to a "jobs" page with a section titled "Where we work," which shows a total of 17,981 employees in the San Francisco area and 1,455 elsewhere in California, out of a total of 20,626 employees; thus, 94% of the total are in California, with 87% at the South San Francisco headquarters.[72]

110. Genentech made its decisions regarding the packaging of the products at issue at its headquarters in South San Francisco, where all of its principal executives are located.

111. Genentech has a seven-member Executive Committee.[73] All members of the Executive committee are based in California: Chief Executive Officer Bill Anderson; Ed Harrington, Chief Financial Officer;[74] Sandra Horning, Executive Vice President, Global Development and Chief Medical Officer;[75] Michael Varney, Executive Vice President, Genentech Research and Early Development;[76] Sean Johnston, Senior Vice President and General Counsel;[77] Kimball Hall, Senior

[70] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf (accessed 2/18/2019).

[71] https://www.gene.com/contact-us/connect-with-us (accessed 2/18/2019).

[72] https://www.linkedin.com/company/genentech/jobs/ (accessed 2/18/2019).

[73] https://www.gene.com/about-us/leadership/executive-committee (accessed 12/11/2018).

[74] https://www.linkedin.com/in/ed-harrington-190a894/ (accessed 2/18/2019).

[75] https://www.linkedin.com/in/sandra-horning-11090788/ (accessed 2/18/2019).

[76] https://www.linkedin.com/in/mike-varney-27114b1/ (accessed 2/18/2019).

[77] https://www.martindale.com/south-san-francisco/california/sean-a-johnston-271855-a/ (accessed 2/18/2019).

Vice President, Manufacturing Biologics Drug Substance;[78] and Nancy Vitale, Senior Vice President of Human Resources, Genentech and Regional Human Resources Head, North America.[79]

112. Genentech's LinkedIn site shows that the following key employees responsible for Genentech's product development, product strategy, and marketing of the subject medicines are located in the San Francisco area: the Senior Vice President, Global Product Strategy Oncology[80]; the Senior Vice President, Global Strategy, Immunology[81]; the Vice President of Global Product Development, Hematology/Oncology;[82] the Vice President responsible for development of Avastin[83]; the Medical Director of Global Product Development[84]; the Marketing Director for Genentech BioOncology (Cancer Immunotherapy)[85]; the Senior Product Manager and Product Manager for Avastin Marketing[86]; the Director of Marketing for Genentech's "HER2" products, including Kadcyla[87]; the Senior Product Manager for Xolair Marketing[88]; and an employee with "[o]verall leadership to over 30 marketers accountable for all marketing aspects of Genentech Hematology, including for Rituxan.[89] Many other Genentech employees with responsibilities for product

[78] https://www.linkedin.com/in/kimball-hall-a6133012/ (accessed 2/18/2019).

[79] https://www.linkedin.com/in/nancy-vitale-a144bb/ (accessed 2/18/2019).

[80] https://www.linkedin.com/in/cindy-perettie-69623b1/ (accessed 2/18/2019).

[81] https://www.linkedin.com/in/frank-lee-9b446b8/ (accessed 2/18/2019).

[82] https://www.linkedin.com/in/nancy-valente-m-d-46461bb/ (accessed 2/18/2019).

[83] https://www.linkedin.com/in/philippe-bishop-aratinga-bio/ (accessed 2/18/2019); he had this position from 2008-2009).

[84] https://www.linkedin.com/in/ted-omachi-a773964/.

[85] https://www.linkedin.com/in/william-f-waas-2a8331a/ (accessed 2/18/2019). As noted above, Avastin, Kadcyla and Rituxan are biooncology drugs.

[86] https://www.linkedin.com/in/brianjpetteys/ and https://www.linkedin.com/in/karyn-heffernan-66526267/ (accessed 2/18/2019).

[87] https://www.linkedin.com/in/michelle-kunkel-mba-b-s-75364413/ (accessed 2/18/2019).

[88] https://www.linkedin.com/in/manoj-warrier-078b913/ (accessed 2/18/2019).

[89] https://www.linkedin.com/in/nnazmi/ (accessed 2/18/2019).

management, marketing, and development of the products at issue are located in the San Francisco area.[90]

113. According to Genentech's website, Genentech's Pharma Technical North America (PTNA) Operations group, headed by Genentech's Global Head of Technical Operations Tim Moore is responsible for packaging its products into vials. [91] Tim Moore is located in the San Francisco Bay area.[92]

CLASS ACTION ALLEGATIONS

114. Plaintiff brings this action on behalf of himself and as representatives of all others similarly situated. Pursuant to Rules 23(a), (b)(2), and/or (b)(3) of the Federal Rules of Civil Procedure, Plaintiff seeks certification of the following class initially defined as follows:

> *All end payors who, during the Class Period, paid for Avastin, Rituxan, Kadcyla or Xolair, a portion of which was discarded because the quantity in the vials exceed the patient's dose (the "Class").*

115. For purposes of the above class definition, "Class Period" encompasses the applicable period of limitations, as well as the period beginning with the filing of this lawsuit and ending on the date notice is sent to the class.

116. Excluded from the Class is Genentech, any entity in which Genentech has a controlling interest, is a parent or subsidiary, or which is controlled by Genentech, and the officers, directors, affiliates, legal representatives, predecessors, successors, and assigns of Genentech. Also excluded from

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[90] https://www.linkedin.com/in/erikhaghjoo/, https://www.linkedin.com/in/brooke-aghajani-2144277/, https://www.linkedin.com/in/thomasvanstavern/, https://www.linkedin.com/in/manoj-warrier-078b913/, https://www.linkedin.com/in/kerstin-schmidt-3ab0687/, https://www.linkedin.com/in/michaeltancer/, https://www.linkedin.com/in/tricia-kim-280212b/, https://www.linkedin.com/in/michelle-dinapoli-73593a5/, https://www.linkedin.com/in/nick-mascioli-3935625/, https://www.linkedin.com/in/angie-redmann-b636574/, https://www.linkedin.com/in/sinhabrownnisha/, https://www.linkedin.com/in/stephanie-wang-570baa5/, https://www.linkedin.com/in/lynn-siu-346575b/, https://www.linkedin.com/in/thomasvanstavern/, https://www.linkedin.com/in/karen-dittrich-003222a/, https://www.linkedin.com/in/uthragopal/, https://www.linkedin.com/in/venu-vittaladevuni-426408/, https://www.linkedin.com/in/wei-liu-b772025/ (all accessed 2/18/2019).

[91] https://www.gene.com/careers/professional-areas/technical-operations (accessed 2/18/2019).

[92] https://www.linkedin.com/in/timothy-moore-65282820/ (accessed 2/18/2019).

the Class are counsel and members of the immediate families of counsel for Plaintiff as well as the judges and court personnel in this case and any members of their immediate families.

117. Plaintiff reserves the right to amend or modify the above class definition with greater specificity or division into subclasses after having had an opportunity to conduct discovery.

118. This action has been brought and may be properly maintained on behalf of the Classes proposed herein under Rule 23 of the Federal Rules of Civil Procedure.

119. **Numerosity**. Fed. R. Civ. P. 23(a)(1). The exact number of Class Members is currently unknown to Plaintiff, but the total number of Class Members is so numerous that joinder of all Class Members would be impracticable.

120. **Commonality and Predominance**. Fed. R. Civ. P. 23(a)(2) and (b)(3). There are questions of law and fact common to the Class that predominate over any questions affecting individual members of each respective class. These common questions of law and fact include, without limitation:

A. Does Genentech sell the subject medicines in vials that are too large for the needs of patients so that large portions must be thrown away?

B. Do patients and their third-party payors pay for the portions of the subject medicines that must be thrown away?

C. Can Genentech reduce the amount of waste by selling its products in smaller vial sizes?

D. Do Genentech's alleged practices violate the unlawful and/or unfairness prongs of California's Unfair Competition Law (Bus. & Prof. Code, §§ 17200, *et seq.*)?

E. Are Plaintiff and Class Members entitled to be reimbursed for the sums they paid for the portions of the subject medicines that must be discarded?

121. **Typicality**. Fed. R. Civ. P. 23 (a)(3). Plaintiff's claims are typical of the claims of the Class he seeks to represent. Plaintiff and all Class Members were exposed to uniform practices and sustained injuries arising out of and caused by Genentech's conduct.

122. **Adequacy of Representation.** Fed. R. Civ. P. 23(a)(4). Plaintiff is an adequate representative of the Class and has no conflict of interest with other class members. Plaintiff's

attorneys are experienced in this type of litigation and will prosecute the action adequately and vigorously on behalf of the Class.

123. **Appropriateness of injunctive relief.** Because Genentech's practices apply to all patients who are administered the subject medicines, Genentech has acted on grounds that apply generally to the Class, so that final injunctive relief is appropriate respecting the Class as a whole.

124. **Superiority.** Fed. R. Civ. P. 23(b)(3). A class action is superior to other available methods for fairly and efficiently adjudicating the controversy. Since the amount of each individual Class Member's claim is small relative to the complexity of the litigation, and due to the financial resources of Genentech, no Class Member could afford to seek legal redress individually for the claims alleged herein. Therefore, absent a class action, Class Members will continue to suffer losses and Genentech's misconduct will continue without remedy. Even if Class Members themselves could afford such individual litigation, the court system could not. Given the complex legal and factual issues involved, individualized litigation would significantly increase the delay and expense to all parties and to the Court. Individualized litigation would also create the potential for inconsistent or contradictory rulings. By contrast, a class action presents far fewer management difficulties, allows claims to be heard which might otherwise go unheard because of the relative expense of bringing individual lawsuits, and provides the benefits of adjudication, economies of scale and comprehensive supervision by a single court. Finally, Plaintiff knows of no difficulty that will be encountered in the management of this litigation which would preclude its maintenance as a class action.

FDA DOES NOT PREVENT GENENTECH FROM INTRODUCING SMALLER VIAL SIZES

125. Genentech has not been constrained by any legal or regulatory restriction of the FDA from introducing vials for the products at issue with less fill volume.

126. As the facts alleged in this Complaint demonstrate, introduction of a smaller vial size (*i.e.*, a vial with a smaller amount of fill) would not have "a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." 21 C.F.R. § 601.12(b)(1). Therefore, such a reduction would not be a "major change" requiring prior FDA approval under 21 C.F.R. § 601.12. Nor does FDA

regulate the economics of drug use. For those reasons, FDA does not require or specifically permit Genentech to make its fill volumes so large that it leads to waste of medication.

127. FDA requires pre-approval of a change in a biological product only if it "has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." 21 C.F.R. § 601.12(b)(1). These changes are called "major changes." 21 C.F.R. § 601.12(b).

128. A manufacturer need not obtain pre-approval of a change in a biological product if it would have a moderate or minimal "potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." 21 C.F.R. § 601.12(c)(1) and (d)(1). Such changes are called "moderate" and "minor" changes, respectively. 21 C.F.R. § 601.12(c) and (d).

129. Reducing the fill volumes in the products at issue would not be a "major" change because it would not have a substantial potential to have an adverse effect on the safety or effectiveness of the products. In fact, it would have no such effect.

130. For example, the Eli Lilly study that reported on the waste-reducing effect of the smaller vial size of Lartruvo stated: "Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use."[93]

131. Specifically, as shown below, reducing the amount of fill of the Genentech products at issue would not have a substantial potential to have an adverse effect on any of the characteristics specified in 21 C.F.R. § 601.12(b)(1) – the identity, strength, quality, purity, or potency of the product – as they may relate to the safety or effectiveness of the product.

132. With respect to identity, FDA requires manufacturers to test the final container of each filling of each lot for "identity." The regulation states: "The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory." 21 C.F.R. § 610.14. That test would identify the product as Avastin, Kadcyla, Rituxan, or

[93] Sheffield *et al.* (2017) at e270.

Xolair regardless of the fill volume. Thus, reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "identity" of the products as it relates to their safety or effectiveness.

133. Similarly, reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "strength" of the products as it relates to their safety or effectiveness. Subchapter F of FDA's regulations, the Subchapter that relates to Biologics, does not contain a definition of "strength." *See* 21 C.F.R. § 600.3 (containing definitions of terms used in Subchapter F and not containing a definition of "strength."). Thus, the appropriate definition is the one in FDA's Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#S (accessed 5/2/2019), which states "The strength of a drug product tells how much of the active ingredient is present in each dosage."

134. The quantity of the active ingredient present in each dosage of the products at issue would be the same regardless of the fill volume, and, therefore, their strength would be unaffected by a change in fill volume. For example, Plaintiff's dose of 772.5 mg of Rituxan from January until June 2016 did not depend on the amount of biologic in the vials (given that the dose was 772.5 mg regardless of the number of vials used). That is, he would have received the same dose regardless of the vials' fills, and, therefore, the strength would be unaffected.

135. Although FDA regulations contain other definitions of "strength," those definitions do not apply to Subchapter F related to biologics. For example, 21 C.F.R. § 314.3 contains a definition of strength, but it states that the definitions in that section apply *only* to Part 314 and Part 320 of the regulations, not to Part 601, which is where the regulation on changes to Biologics is located.

136. Similarly, reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "quality" of the products as it relates to their safety or effectiveness. Neither Subchapter F of FDA's regulations related to Biologics nor FDA's Glossary of Terms contains a definition of "quality." Merriam-Webster's principal definition of

"quality" is "peculiar and essential character."[94] The peculiar and essential character of the products at issue would not change, no matter how much biologic is in the vial. Thus, their quality would not change.

137. With respect to "purity," the regulations on Biologics define it as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances." 21 C.F.R. § 600.3(r). A reduction in fill volume of the products at issue would have no effect on their freedom from extraneous matter, and therefore it would have no effect on their purity as it may relate to safety or effectiveness.

138. With respect to "potency," FDA's definition states: "The word potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." 21 C.F.R. § 600.3(s). Reducing the fill volume in the vials of the products at issue would not affect their ability or capacity to achieve their results, and therefore it would not have a substantial adverse effect on their potency, as it may relate to safety or effectiveness.

139. Nor would reducing the fill volume of the Genentech products at issue be a major change as one affecting product sterility assurance as provided in 21 C.F.R. § 601.12(b)(2)(vi). There are two reasons for that.

140. First, 21 C.F.R. § 601.12(b)(2)(vi) specifies that it is referring to methods and processes, such as sterilization methods. That provision refers to "Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation." *Id.* Genentech would not need to change a sterilization method or do anything to the steps in an aseptic processing operation to reduce the amount of fill in the vial.

[94] Merriam-Webster definition of "quality." https://www.merriam-webster.com/dictionary/quality (accessed 5/2/2019).

141. Second, even if that regulation referred to the use of a different vial or container and stated that such a change would affect sterility assurance, there is no reason why the manufacturer could not use the same vial and simply fill it with a smaller amount. Indeed, that is what FDA would require in that situation. 21 C.F.R. § 601.12(a)(3) states, "Notwithstanding the requirements of paragraphs (b), (c), and (f) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report)." Thus, if using a different vial would require prior approval, the manufacturer would be required to put the smaller fill volume in the existing vial.

142. Reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "quantitative formulation" of the products as it relates to their safety or effectiveness. Neither the regulations nor the FDA website contains a definition of "formulation" or "quantitative formulation," but Oxford Living Dictionaries defines "formulation" as "[a] material or mixture prepared according to a formula."[95] That has nothing to do with the amount of fill in the vial.

143. Furthermore, the way FDA refers to "formulation" shows that it relates to the chemical formulation of the drug, not the amount of the drug in the container. *See*, *e.g.*, 21 C.F.R. § 601.12(b)(2) ("quantitative formulation, including inactive ingredients"); FDA Glossary of Terms ("The Chemical Type represents the newness of a drug formulation or a new indication for an existing drug formulation. For example, Chemical Type 1 is assigned to an active ingredient that has never before been marketed in the United States in any form."):[96] FDA, Inactive Ingredient Search for

[95] https://en.oxforddictionaries.com/definition/formulation (accessed 5/2/2019) (Definition 2; the first definition does not apply in this context).

[96] https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#C (accessed 5/2/2019).

Approved Drug Products: Frequently Asked Questions ("Alcohol is a good example of an ingredient that may be considered either active or inactive depending on the product formulation.").[97]

144. Reducing the fill volume of the Genentech products at issue would not be a major change because of a requirement to change their specifications. "Specification" as used in 21 C.F.R. § 601.12 is defined as:

> the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

21 C.F.R. § 600.3. Nothing in that definition says that the approved quantity of medicine filled into each container is a specification. Instead, it refers to "quality," which, as described above, would be unchanged with a smaller vial.

145. FDA does not prevent manufacturers from introducing smaller vial sizes to keep dosages to a single vial. Although an FDA Guidance document states that "[c]onsumers and/or health care providers should not be routinely required to use more than one vial to administer a typical single dose of the drug product,"[98] this is not a mandatory requirement. FDA states: "The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required."[99].

146. Moreover, Genentech routinely ignores this recommendation and sizes its products so that multiple vials are needed for each treatment. As shown above, the typical or average patient needs four or five vials of Avastin and three vials of Kadcyla and Rituxan each per treatment.

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[97] https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredient-search-approved-drug-products-frequently-asked-questions (accessed 5/2/2019).

[98] FDA Guidance, Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, 2015 WL 4652905, at *3.

[99] *Id.* at *1.

147. Genentech has attempted to mislead the public into believing that it sizes its products to limit a single treatment to a single vial. After this lawsuit was filed, Genentech representative Emily Wang was quoted in the press as saying, "The FDA calls on companies to balance vial contents so that leftover drug is minimized yet also provide enough drug so that more than one vial is rarely needed for a single dose."[100] This is misleading because Genentech does not provide enough drug so that more than one vial is rarely needed for a single dose. More than one vial is invariably, or virtually invariably, needed to meet the dosage levels routinely prescribed to cancer patients using the biologics at issue in this suit.

148. Reducing the fill volume of the Genentech products at issue would not require pre-approval as a major change to the products' labels. To the contrary, the change would only need to be submitted in an annual report (and would not have to be submitted to the FDA before the change was made). The relevant regulation provides:

> An applicant shall submit any final printed package insert, package label, container label, or Medication Guide required under part 208 of this chapter incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:
>
> ***
>
> (B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form;

21 C.F.R. § 601.12.

149. A change in how the products at issue are supplied by reducing the fill volume in their vials would not involve a change in the dosage strength or dosage form because the dosage would remain the same; therefore, such a change would require only a minor amendment to the product labels, one required to be submitted only in an annual report.

150. Plaintiff filed this lawsuit rather than a citizen petition with FDA because FDA is powerless to afford Plaintiff the relief he seeks. FDA regulates only the safety and effectiveness of drugs, not their economics or the fairness of how they are marketed. Under 42 U.S.C. § 262(a)(1)(C),

[100] Hailey Konnath, Genentech Profits Off Wasteful Cancer Drug Vials, Suit Says, Law 360 (Feb. 28, 2019).

its approval of a biologic license is limited to determining whether the product is "safe, pure and potent." FDA states: "All FDA-approved biological products, including reference, biosimilar, and interchangeable products, undergo a rigorous evaluation to ensure that patients can rely on their efficacy, safety, and quality."[101]

151. This fact was confirmed by the committee of the National Academy of Sciences quoted above, which said: "Manufacturers propose dose sizes for marketing, and the FDA only reviews the request for safety considerations [citation omitted]."[102] Members of that committee included a former Chief Medical Officer of the pharmaceutical company Merck & Co., Inc., and a former President and CEO of the pharmaceutical company Genzyme Corporation.

152. Furthermore, even if FDA were authorized to consider economics and the fairness of how a product is marketed, it would be powerless to compel Genentech to introduce smaller vial sizes. It can only approve or disapprove a manufacturer's application. It cannot order changes to the product. Nor could it award restitution to patients and third-party payers for the money they have spent on drugs that necessarily went to waste. All FDA could do would be to order the products taken off the market. Plaintiff does not seek to order these products off the market. He seeks restitution and fair practices.

153. The example of Eli Lilly's biologic cancer drug Lartruvo confirms that a smaller vial size may be introduced without FDA's pre-approval. FDA first approved Lartruvo on October 19, 2016.[103] Its original label shows that it was supplied in only one vial size, 500 mg.[104]

154. As alleged above, four-and-a-half months later, on March 6, 2017, Eli Lilly introduced a vial containing only 190 mg of Lartruvo to reduce the amount of product that went to waste.

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[101] Biosimilar Development, Review and Approval, https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval (accessed 5/3/2019).

[102] Making Medicines Affordable at 99-100.

[103] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761038 (accessed 5/3/2019).

[104] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761038lbl.pdf at 8 (accessed 5/3/2019).

155. According to a response by FDA to a Freedom of Information Act request on June 8, 2017, there was at that time a pending product supplement for the vial size of 190 mg for Lartruvo which FDA had not approved.[105] The 190 mg vial size of Lartruvo had by then been on the market for three months; thus, the change must have been submitted to FDA in a CBE-30 or, perhaps, in an annual report. In either case, the change in vial size did not require FDA's prior approval. Similarly, Genentech would not have needed FDA's prior approval to introduce a smaller vial size of the products at issue.

FIRST CLAIM FOR RELIEF
Violation of California's Unfair Competition Law
(By Plaintiff and the Class Against All Defendants)

156. Plaintiff realleges and incorporates by reference all preceding paragraphs of this Complaint as though fully alleged in this paragraph.

157. Plaintiff brings this claim individually and on behalf of the members of the Class against Genentech under California law.

158. Plaintiff has standing to pursue this cause of action as Plaintiff has suffered injury in fact and has lost money or property as a result of Genentech's actions as delineated herein.

159. Genentech's scheme, as delineated herein, constitutes unlawful and/or unfair business practices in violation of California Business and Professions Code sections 17200, *et seq.*

160. Genentech's practices of selling drugs in quantities that inherently lead to wasted amounts of medicine, causing substantial injury to Plaintiff and the Class who are forced to purchase large amount of medications that they do not and cannot use. As set forth above, the financial injury to Plaintiff alone from Genentech's scheme runs into the thousands of dollars. Genentech's scheme also means that there is no way for Plaintiff and the Class to avoid these losses since they must purchase the medication and can only purchase vials at the sizes that Genentech has decided to provide – regardless of the waste that will necessarily result. Likewise, the injuries suffered by Plaintiff are not outweighed by countervailing benefits to consumers or competition. In fact, there are no

[105] Letter from Sarah B. Kotler, Director, Division of Freedom of Information, FDA, to Richard Cornfeld (June 8, 2017). (Ex. E).

countervailing benefits to consumers or competition from supplying cancer and other medications in sizes that are too large for patients to fully use.

161. Genentech's business practices, as alleged herein, violate the "unlawful" prong of California Business & Professions Code sections 17200, *et seq.* because they violate, *inter alia*, Section 5(a)(1) of the FTC Act, 15 U.S.C. § 45(a)(1).

162. Genentech's business practices, as alleged herein, violate the "unfair" prong of California Business & Professions Code sections 17200, *et seq.* because, *inter alia*,: (i) the utility of Genentech's scheme is significantly outweighed by the gravity of the harm the scheme imposes on Plaintiff and the Class; (ii) the injury suffered by Plaintiff and the Class as a result of Genentech's scheme is substantial and is not one that Plaintiff and the Class could have reasonably avoided; and (iii) Genentech's scheme runs counter to legislatively declared and public policy.

163. These acts and practices of Genentech violate established public policy as expressed, *inter alia*, by the FTC's Policy Statement on Unfairness.

164. These acts and practices of Genentech are immoral, unethical, oppressive, unscrupulous, and/or substantially injurious to consumers

165. The consumer injury resulting from Genentech's acts and practices is substantial, not outweighed by any countervailing benefits to consumers or to competition, and not an injury that the consumers themselves could reasonably have avoided.

166. Accordingly, Genentech has violated, and continues to violate, California Business and Professions Code section 17200's proscription against engaging in unlawful business acts or practices.

167. As a direct and proximate result of Genentech's unlawful and/or unfair business practices, Plaintiff and the Class have suffered injury in fact and lost money or property, in that they spent money or property on medication that was unwanted and unneeded.

168. Pursuant to California Business and Professions Code section 17203, Plaintiff and the Class seek an order of this court enjoining Genentech from continuing to engage in unlawful and/or unfair business practices and any other act prohibited by law, including those acts set forth in the complaint.

169. Plaintiff and the Class also seek an order requiring Genentech to make full restitution of all monies wrongfully obtained from Plaintiff and the Class.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff, on behalf of himself and the Class, prays judgment against Genentech as follows:

A. An order certifying appropriate Classes and/or Subclasses, designating Plaintiff as the class representative and the undersigned counsel as class counsel;

B. An order enjoining Genentech from continuing to engage in the practices complained of herein, including but not limited to requiring that Genentech cease selling subject medicines only in quantities that necessarily lead to waste;

C. An award of restitution, damages, and disgorgement to Plaintiff and the Class in an amount to be determined at trial;

D. An order requiring Genentech to pay both pre- and post-judgment interest on any amounts awarded, as allowed by law;

E. An award of costs and attorneys' fees, as allowed by law, including but not limited to section 1021.5 of the Code of Civil Procedure; and

F. Such other or further relief as may be appropriate.

Dated: May 17, 2019

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DEMAND FOR JURY TRIAL

Plaintiff, individually and on behalf of all others similarly situated, hereby demands a trial by jury of any and all issues in this action so triable of right.

Dated: May 17, 2019

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Exhibit A

thebmj

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ANALYSIS

Overspending driven by oversized single dose vials of cancer drugs

Peter B Bach and colleagues call for an end to contradictory regulatory standards in the US that allow drug manufacturers to boost profits by producing single dose vials containing quantities that increase leftover drug

Peter B Bach *professor director*[1], Rena M Conti *associate professor*[2], Raymond J Muller *associate director of pharmacy services*[3], Geoffrey C Schnorr *project coordinator*[1], Leonard B Saltz *professor chair of pharmacy and therapeutics committee*[1 4]

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Even though reducing waste in healthcare is a top priority, analysts have missed the waste that can be created when expensive infused drugs are packaged containing quantities larger than the amount needed.[1 2] This is particularly true for drugs for which dosage is based on a patient's weight or body size and that come in single dose packages. These drugs must be either administered or discarded once open, and because patients' body sizes are unlikely to match the amount of drug included in the vial, there is nearly always some left over. The leftover drug still has to be paid for, even when discarded, making it possible for drug companies to artificially increase the amount of drug they sell per treated patient by increasing the amount in each single dose vial relative to the typically required dose.

Increasing the amount of drug sold per treated patient also increases profits to doctors and hospitals in the United States. Under a system nicknamed "buy and bill," doctors and hospitals buy single dose vials of drugs and then bill insurers or patients when they are used. The bill includes a percentage based mark-up which can vary widely, but even low percentages can equate to large amounts of money given that many of the drugs cost thousands of dollars per vial.

Although doctors and hospitals sometimes use leftover drug to treat a subsequent patient, thus reducing the amount of leftover drug for which they bill, this practice is very limited. Safety standards from the US Pharmacopeial Convention permit sharing only if leftover drug is used within six hours, and only in specialised pharmacies.[3-5]

We analysed spending on cancer drugs that are packaged in single dose vials and dosed based on body size in the United States to estimate the extent of the problem. We focused on the US because, unlike in most other Western countries, the government plays no role in how drugs are priced and doctors and hospitals can profit from leftover drugs. Although similar problems exist with other drugs, cancer drugs are expensive and they constitute the largest single category of specialty drug spending.[6] Moreover, cancer drugs often have narrow therapeutic and toxicity windows, meaning that dosing is commonly based on a patient's body size.

How big is the problem?

We examined the top 20 cancer drugs that are dosed by body size and packaged in single dose vials (based on 2016 projected sales), which collectively account for 93% of all sales of such drugs. We calculated the total amount of leftover drug and resulting 2016 US revenues for each drug using the method shown in fig 1⇓. In brief, we estimated how often vial sharing occurred by examining how often claims filed with the Medicare program included amounts of drug that did not total the full contents of the vial. We then calculated the most efficient way to combine available vial sizes to achieve the lowest US Food and Drug Administration approved dose in a representative sample of the US population derived from the National Health and Nutrition Examination Survey.[7] After correcting for vial sharing percentage, and adjusting the population to mirror a cancer patient population, we apportioned projected 2016 US revenues to administered or leftover drug.[8 9] When calculating the effect of vial sharing we assumed that doses that were not multiples of available vial sizes had no leftover drug, an assumption that made our estimates of leftover drug conservative.

Table 1⇓ shows the leftover drug from the packaging approaches for the 20 drugs. We estimate total US revenue from these drugs

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to be $18bn (£12.5bn; €16bn) in 2016, with 10% or $1.8bn from discarded drug. The extent and cost of leftover drug varies according to market size and available vial sizes. For example, in 2016, 7% of $3.9bn in rituximab sales will be on discarded drug, totaling $254m, while 33% of $697m in carfilzomib sales will be discarded, totaling nearly as much, $231m. Sensitivity analyses suggested our results were robust. If every person received the highest dose approved by the FDA, revenue from discarded drugs falls to $1.4bn; if every cancer patients weighed 10% less than the survey participants, the estimate rises to $2bn.

The proportion of drug left over varies from 1% to 33%. Between these extremes are drugs such as bevacizumab, which comes in both 100 mg and 500 mg vials, and ipilimumab, which comes in both 40 mg and 100 mg. About 9% and 7% of these drugs, respectively, is left over. Yet small percentages can still lead to large dollar amounts. The October 2015 Medicare Average Sales Price files show that a dose of ipilumumab might cost $29 000,[10] meaning that the 7% left over would generate an additional $2000 in revenue for the company for each vial sold.

How drug quantity affects profits and waste

The effect of different approaches to packaging for single dose vials is illustrated by the two drugs bendamustine and bortezomib. Bendamustine, a drug for leukemia, is sold in a broad array of single dose vials (25, 45, 100, and 180 mg) that can be combined to reach its dose of 100 mg/m^2 nearly precisely (fig 2⇓). Vial combinations cover every 5 mg interval across the typical adult dose range of 110 mg to 310 mg, with the exception of 130 mg and 155 mg. We calculate that only 1% of bendamustine is wasted. Bortezomib on the other hand, a drug to treat multiple myeloma, is available in the US in only a 3.5 mg vial, much larger than the average required dose, which we calculate to be 2.5 mg based on the drug's dose of 1.3 mg/m^2 and the average weight of a cancer patient. Our estimate is that 27% to 30% of bortezomib sales in the US are related to leftover drug equating to $309m. The large vial size of bortezomib seems to be unique to the US market. The drug is sold in 1 mg vials in the UK.[11]

Pembrolizumab provides another example of how vial sizes can influence revenues. When it was initially approved in the US in September 2014, the drug was sold in 50 mg vials (as a powder that needs to be reconstituted into a liquid). But in February 2015 the manufacturer introduced a larger 100 mg vial (as a liquid) and stopped distributing the 50 mg vials to the US market. Five months later, in July 2015, pembrolizumab was approved in Europe, where it is sold in the smaller 50 mg vials as a powder.

The increased revenue from the change is substantial. Consider a 70 kg patient who requires a dose of 140 mg (the drug is dosed at 2 mg/kg). When the drug was sold in 50 mg vials, reaching the desired dose would require three 50 mg vials and leave 10 mg unused. But with only 100 mg vials available, 60 mg is left over. According to the Medicare Not Otherwise Classified October 2015 file, which lists Medicare's reimbursement rates for these drugs, each milligram of pembrolizumab costs around $50. In this example the change in vial size alone increases the revenues for the company from leftover drug by sixfold, from $500 to $3000, for a single dose. We estimate that the additional revenue to the company from the packaging change over the next five years will be $1.2bn, which comes on top of the $1.2bn they would have gained from leftover drug with the 50 mg package (table 2⇓). Similarly, by only selling bortezomib in the US in the larger 3.5 mg vials rather than the 1 mg vials sizes available in Europe, the manufacturer, Millennium, will increase its 2016 US revenues by $130m (data not shown).[11]

Effect on hospitals and patients

We have focused on how much money companies earn in terms of revenues from leftover drug, not how much payers and patients are spending on them, which is a larger number due to the fact that distributing intermediaries and treating doctors and hospitals mark-up drugs when they bill for them. The mark-up varies considerably. In public insurance programs such as the Federal Medicare program the mark-up set by Congress is 6% and is currently 4%. For commercial insurance, which is the more common coverage in the United States, payers have reported that they pay mark-ups to doctors and hospitals in the order of 22% and 142%, respectively.[12] In hospitals that use the distribution channel 340B, mark-ups in the Medicare program have been estimated to be 58%.[13-15] The mark-up for commercially insured patients at these types of hospitals is even greater. So although it is hard to precisely estimate the additional profit that will come to doctors and hospitals from billing for leftover cancer drugs, our estimate is that it will almost certainly exceed $1bn in 2016.

The additional costs to patients, who are charged for leftover drug just as they are for drug they have received is also likely to be substantial. Medicare Part B, covering roughly half of cancer patients, includes 20% coinsurance with no upper limit, and 14% of beneficiaries have no additional coverage for their coinsurance.[16] Private insurance generally has out of pocket maximums that many patients with cancer reach regardless.

Although we focused on cancer, the problem of mismatched single dose vials and doses is not unique to the disease. The asthma drug omalizumab has approved doses in 75 mg intervals, but the company only sells 150 mg vials in the United States, even though it has an approved 75 mg vial size. The drug infliximab, one of the largest selling drugs in the United States with expected 2015 revenues of $4.3bn, is available in only 100 mg single dose vials. It is also dosed based on body size and using the same methods we applied to the cancer drugs, this packaging generates around $500m in additional revenues from leftover drug.

How can we stop the waste?

Regularly and systematically discarding expensive drugs is antithetical to efforts to reduce spending on healthcare services that provide no value. Policy makers should therefore explore approaches that would reduce or eliminate paying for leftover drug. Current regulatory standards could be viewed as contradictory, or at least as ambiguous (box). The FDA calls on companies to balance vial contents so that leftover drug is minimized yet they should also provide enough drug that more than one vial is rarely needed for a single dose.[17] Guidance on vial sharing is also inconsistent. The Centers for Medicare and Medicaid Services essentially encourages it; the Centers for Disease Control and Prevention states that it is unsafe (box).[18 19]

Several policy options merit exploration. Regulators could require manufacturers to provide drugs in a reasonable set of size options to ensure the amount of wasted drug is low, say 3%. This is achievable, as table 3⇓ shows. If all of our suggestions were adopted, it would lower revenue from leftover drug from $1.8bn to $400m and, including the reductions to doctor and hospital mark-ups on leftover drug, would save around $2bn in total. An alternative would be to leave

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Federal agency guidelines and advisories regarding proper drug quantity and use of drugs contained in single dose vials (SDVs)

FDA guideline[20]—"Significantly more drug than is required for a single dose may result in the misuse of the leftover drug product. Similarly, the need to combine several single-dose vials for a single patient dose may lead to medication errors and microbial contamination"

Centers for Medicare and Medicaid Services advisory[21]—"It is permissible for healthcare personnel to administer repackaged doses derived from SDVs to multiple patients, provided that each repackaged dose is used for a single patient in accordance with applicable storage and handling requirements"

Centers for Disease Control and Prevention guideline[22]—"Vials labeled by the manufacturer as 'single dose' or 'single use' should only be used for a single patient. These medications typically lack antimicrobial preservatives and can become contaminated and serve as a source of infection when they are used inappropriately"

manufacturers free to select their vial sizes but also require them to refund the cost of leftover drug. This could be achieved through certified disposal and a virtual return.

One pattern sometimes seen in clinical practice is to round up doses to the quantity in the full vial, thus changing dosing from body sized based to "flat" or "fixed" dosing. The approach is problematic not only because it leads some patients to receive too high a dose and others too low when compared to the FDA approved dose, but also because it does not reduce spending on leftover drug. It merely changes clinician behavior from discarding leftover drug to infusing leftover drug into patients.

Policy makers should also revisit the current FDA guidance on the appropriate packaging of infused drugs in single dose vials and encourage the FDA, CDC, Centers for Medicare and Medicaid Services, and US Pharmacopeial Convention to reconcile their views on vial contents and vial sharing. Such steps could lead to savings for our healthcare system without sacrificing health outcomes. Opportunities to eradicate waste of this kind are rare.

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Contributors and Sources: PBB is guarantor, and is the director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center (MSKCC). Rena M. Conti is a health economist at the University of Chicago. Raymond J. Muller is the Associate Director of Pharmacy Services at MKSCC, and Geoffrey C. Schnorr was a project coordinator in the Center for Health Policy and Outcomes at MSKCC. Leonard B. Saltz is the Chair, Pharmacy and Therapeutics Committee at MSKCC. All authors analyzed and interpreted the data. PBB drafted the manuscript. PBB, RMC, RJM, GCS, and LBS revised the manuscript and all authors approved the final version. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing Interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: PBB reports personal fees from Association of Community Cancer Centers, America's Health Insurance Plans, AIM Specialty Health, American College of Chest Physicians, American Society of Clinical Oncology, Barclays, Defined Health, Express Scripts, Genentech, Goldman Sachs, McKinsey and Company, MPM Capital, National Comprehensive Cancer Network, Novartis, Biotechnology Industry Organization, *American Journal of Managed Care*, Boston Consulting Group, Foundation Medicine; LBS reports grants from Taiho Pharmaceuticals; RJM reports personal fees from Amgen, Hospira, Seattle Genetics, Sunesis, Amneal Biosciences, Magellan Medication Management System, and is an uncompensated member of the national clinical advisory committee for the Institute of Safe Medication Practices.

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Key messages

- Many infused cancer drugs are packaged in single dose vials but dosed based on body size, often resulting in leftover drug
- All the drug in the vial has to be paid for, making wasted drug a source of unnecessary spending
- Drug companies will earn around $1.8bn from leftover cancer drugs in the United States in 2016
- Manufacturers should be required to package drugs in quantities that allow better matching with required doses or enable virtual return of leftover drug

Tables

Table 1| Top 20 infused cancer drugs based on projected 2016 sales sold in single dose vials and dosed based on patient body size

Drug (brand name), year of FDA approval	Dose of first approved indication (highest approved dose at any time)	Amount of drug in available single dose vials (discontinued vial sizes)*	Vial sharing			2016 expected sales ($m)	2016 expected revenue from leftover drug ($m)
			% of leftover drug using only full vials	% doses with vial sharing	% of leftover drug adjusted for frequency of vial sharing†		
Paclitaxel protein bound (Abraxane), 2005	Breast 260 mg/m^2	100	9	16	8	960.77	76.72
Brentuximab vedotin (Adcetris), 2011	Lymphoma 1.8 mg/kg	50	15	36	10	292.18	29.15
Pemetrexed (Alimta), 2004	Mesothelioma/lung 500 mg/ m^2	100, 500	5	16	4	1269.04	54.64
Bevacizumab (Avastin), 2004	Colorectal 5 (15) mg/kg	100, 400	11	19	9	3159.32	284.49
Ramucirumab (Cryamza), 2014	Gastric 8 (10) mg/kg	100, 500	7	16‡	6	471.55	28.78
Cetuximab (Erbitux), 2004	Head/neck 250 (400) mg/m^2	100, 200	6	19	5	570.22	29.18
Asparaginase Erwinia chrysanthemi (Erwinaze), 2011	All 25000 IU/ m^2	10000	10	16‡	8	170.40	14.13
Eribulin (Halaven), 2010	Breast 1.4 mg/ m^2	1	15	18	13	167.71	21.85
Cabazitaxel (Jevtana), 2010	Prostate 25 mg/m^2	60	23	12	21	127.96	26.89
Ado-trastuzumab emtansine (Kadcyla), 2013	Breast 3.6 mg/kg	100, 160	7	16‡	6	413.96	23.66
Pembrolizumab (Keytruda), 2014	Melanoma 2 mg/kg	(50), 100	24	16‡	21	943.07	197.94
Carfilzomib (Kyprolis), 2012	Myeloma 20 (27) mg/ m^2	60	37	16‡	33	697.65	231.45
Filgrastim (Neupogen), 1991	Neutropenia 5 (10) µg/kg	300, 480	17	0§	17	623.85	106.01
Irinotecan liposome (Onivyde), 2015	Pancreatic 70 mg/m^2	43	7	16	6	118.09	7.13
Nivolumab (Opdivo), 2014	Melanoma 3 mg/kg	40, 100	4	16‡	3	2078.63	68.93
Rituximab (Rituxan), 1997	Non-Hodgkin's lymphoma 375 (500) mg/m^2	100, 500	7	0§	7	3852.75	253.85
Bendamustine (Treanda), 2008	Chronic lymphocytic leukemia 100 (120) mg/ m^2	25, 45, 100, 180	1	6	1	563.44	7.38
Panitumumab (Vectibix), 2006	Colorectal 6 mg/kg	100, 200, 400	10	17	8	237.41	18.72
Bortezomib (Velcade), 2003	Myeloma:1.3 mg/ m^2	3.5	30	16	27	1160.64	308.74
Ipilimumab (Yervoy), 2011	Melanoma 3 mg/kg	50, 200	10	22	7	620.22	46.47
Total	—	—	—	—	—	18 498.86	1836.11

*All amounts in mg except for filgrastim (µg) and asparaginase (IU). Filgrastim also sold in single dose prefilled syringes.

†Based on (discarded percentage assuming full vials×proportion of full vials)/((discarded percentage assuming full vials×proportion of full vials)+average dose).

‡Based on median of drugs for which there were available data.

§Billed in full vial or full prefilled syringe units.

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Table 2| **Projected revenue from sales of pembrolizumab comparing scenarios with revenue only from administered drug, revenue based on 50 mg vial sizes with reimbursement for leftover drug, and revenue based on 100 mg vial sizes with reimbursement for leftover drug. Data based on pooled analyst estimates compiled by Defined Health.**

Year of sales	Revenue from dose only ($m)	Revenue from dose and leftover using 50 mg vials ($m)	Revenue from dose and leftover using 100 mg vials ($m)
2016	762	862	964
2017	1335	1510	1690
2018	1991	2253	2520
2019	2346	2654	2969
2020	2687	3040	3401
Total	9121	10 320	11 544

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Table 3| Proposed additional single dose vial sizes to reduce the amount of waste on leftover drug for 18 out of 20 top selling cancer drugs in our analysis for which we propose one additional size and estimation of effect on waste in 2016

Generic name	Currently available vial sizes (mg)	Proposed additional vial size	Estimated waste in 2016 ($m)		Value of drug in additional vial ($)*
			With existing vials	With additional vial	
Paclitaxel protein bound	100	30	77	8	293
Brentuximab vedotin	50	10	29	6	1193
Pemetrexed	500, 100	60	55	11	367
Bevacizumab	400, 100	20	284	60	139
Ramucirumab	500, 100	40	29	6	432
Cetuximab	200, 100	50	29	15	267
Asparaginase Erwinia chrysanthemi	10000†	3000†	14	2	1129
Eribulin	1	0.25	22	6	256
Cabazitaxel	60	2.5	27	3	372
Ado-trastuzumab emtansine	160, 100	20	24	12	584
Pembrolizumab	100, (50)‡	10	198	24	457
Carfilzomib	60	2.5	231	19	78
Irinotecan liposome	43	10	14	1	389
Nivolumab	100, 40	10	69	35	254
Rituximab	500, 100	40	254	53	300
Panitumumab	400, 200, 100	30	19	2	303
Bortezomib	3.5	0.25	309	48	117
Ipilimumab	200, 50	10	46	10	1388
Total	—	—	1843.11	434.25	—

*Based on October 2015 ASP files.[10]

†International Units.

‡No longer marketed.

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Figures

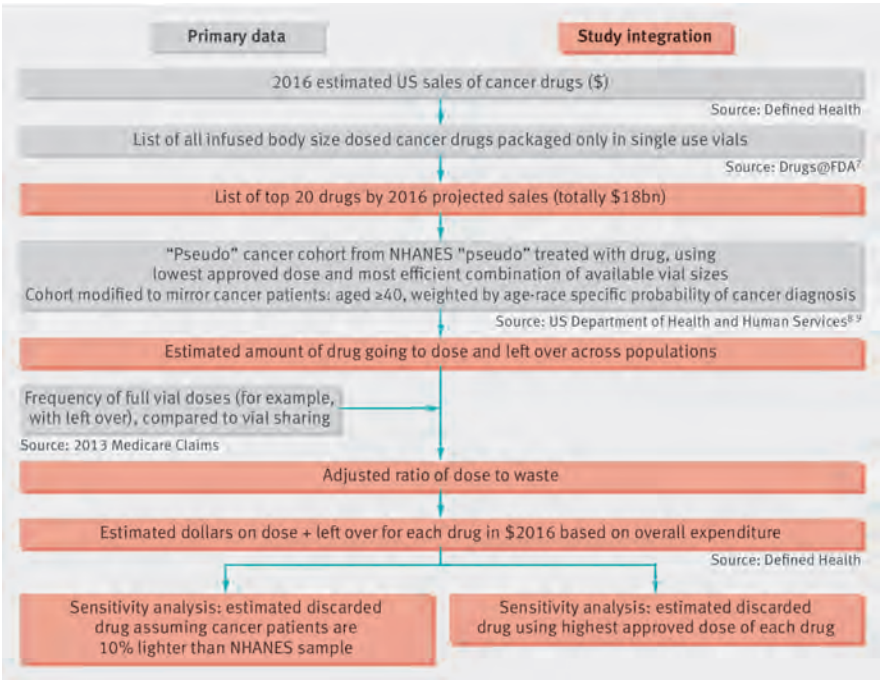

Fig 1 Study flowchart

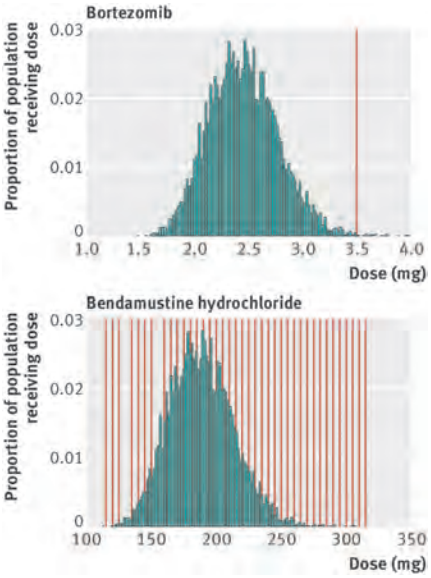

Fig 2 Distribution of FDA approved dose (green histogram) in the US population of cancer patients, and available combinations of full vial contents (red lines) to achieve that dose for bortezomib (top) and bendamustine (bottom)

Exhibit B

Minimization of olaratumab drug waste using real-world data

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Purpose. Results of a study in which population-based body weight and body surface area (BSA) data were used for vial size optimization to reduce drug waste associated with administration of the i.v. anticancer agent olaratumab are reported.

Methods. A retrospective observational study was conducted to determine weight and BSA distributions in a large sample of U.S. oncology patients using data from a large electronic medical record database. Body weight and BSA values at the time of initial systemic anticancer therapy were used to compute olaratumab dose requirements in a cohort of patients with soft tissue sarcoma; those data were analyzed to derive estimates of drug waste likely to result from the use of various proposed olaratumab vial sizes in combination with an existing 500-mg size. Weight and BSA distributions were calculated for additional cohorts of patients with 7 other cancer types.

Results. Median weight values in men (n = 1,179) and women (n = 1,078) with soft tissue sarcoma were 82.55 kg (interquartile range [IQR], 72.58–95.53 kg) and 68.69 kg (IQR, 58.51–84.28 kg), respectively. Modeling of olaratumab dosing scenarios indicated that use of the 500-mg vial only would result in estimated average drug waste of 234 mg per patient per administration; analysis of various potential vial size combinations showed that waste could be reduced by 87.6% with the addition of a 190-mg vial size.

Conclusion. Analysis of real-world patient weight and BSA data allowed olaratumab vial size optimization to enable maximal dosing flexibility with minimal drug waste.

Keywords: antineoplastic agents/therapeutic use, body weight, drug packaging, drug waste, electronic health records, neoplasms/drug therapy

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The cost of cancer care in the United States is projected to increase to more than $157 billion by 2020.[1] A number of factors contribute to the growth in cancer care costs, including the increasing incidence and prevalence of cancer in an aging population, advancements in treatments and technology, and the adoption of novel targeted therapies.[1-3] With increasing costs of oncology care, cost-containment strategies are important. Cancer care facilities and providers are seeking to redirect resources toward higher-value care and minimize costs and wastage during the delivery of oncology care.[2-4]

The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures. Cancer care facilities and providers can incur serious economic losses as a result of inefficient drug usage and waste resulting from the disposal of unused or partially used ampules, vials, and prepared syringes.[5-8] Although the economic loss attributable to wastage of oncology drugs is not fre-

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quently reported, in some facilities drug wastage has been estimated to account for more than 8% of the annual drug expenditure,[9] and several facilities have reported savings of 4–5% of annual drug expenditures with the implementation of waste-minimization protocols.[6,10,11] Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use.[6]

Vial size and limited beyond-use dating (i.e., issues with stability and sterility) are often cited as the 2 main causes of oncology drug wastage.[5,6,9,12] Oncology drugs are frequently marketed in large vial sizes or even a single vial size.[5,13] However, it is common practice among clinicians to calculate doses to the nearest milligram according to body surface area (BSA) or weight, and available vial sizes often are not well suited to cost-efficient administration of the drug dosages possible across the distributions of patient weight and BSA.[6,7] In addition, many oncology drugs, especially monoclonal antibodies, are packaged preservative free and allow for only single uses with short expirations.[14,15] Unused partial vials can amount to considerable drug waste.

Physicians and pharmacists have called for cooperation with manufacturers to produce more suitable final vial sizes.[6,7] Manufacturers can help reduce waste by producing appropriate and multiple vial sizes based on the distribution of body sizes across the targeted patient population. However, vial size is typically determined prior to Phase III studies by coupling effective doses extrapolated from Phase I or II studies with mean BSA or weight data from trial populations. Little published literature with population-based estimates of BSA or weight for adult patients diagnosed with cancer is available, and estimates based on data from clinical trial participants may not be representative of current patients in real-world clinical practice. The weight and BSA values used in dosage calculations also can have important consequences for pharmacy budget projections, health technology assessments, and payer budget impact models.[13] Population-based weight and BSA distributions would enable better estimations of potential drug wastage and, more importantly, allow manufacturers to calculate and produce optimal vial sizes for a target patient population in actual clinical practice.

The first objective of the study described here was to provide healthcare providers, health technology assessors, payers, and manufacturers with population-based estimates of weight and BSA for U.S. patients with cancer using electronic medical record (EMR) data from outpatient community oncology practices. The cancers of interest were soft tissue sarcoma, multiple myeloma, and breast, colorectal, lung, ovarian, prostate, and gastric cancers. These results could be used as inputs to estimate wastage and drug costs as well as to determine dosage forms and vial sizes for drugs in development. The second objective of the study was to demonstrate the use of real-world BSA and weight data to optimize the size of a planned additional product container for olaratumab (Lartruvo, Eli Lilly and Company), a platelet-derived growth factor receptor α–blocking antibody that received accelerated Food and Drug Administration (FDA) approval in October 2016 for use (in combination with doxorubicin) for the treatment of patients with soft tissue sarcoma. Olaratumab dosing is based on patient weight (in milligrams per kilogram).[16]

At the time of our study, olaratumab was undergoing Phase III clinical testing. A 500-mg/50-mL vial size had already been evaluated and was in production, but a second vial size was explored with the goal of reducing drug waste and overall costs for institutions. The olaratumab research presented here illustrates how real-world weight data on patients with cancer were used to determine the optimal volume for a planned new olaratumab vial size and quantify the reduction in drug waste associated with the addition of the new vial size.

KEY POINTS

- Population-based estimates of mean body weight and body surface area (BSA) values in oncology patients were derived for use in health economics evaluations of anticancer drugs.
- Manufacturers can help reduce drug waste by producing multiple vial sizes based on weight and BSA distributions across the targeted patient population in actual clinical practice.
- A case study of olaratumab dosing indicated that vial size optimization would result in an 87.6% reduction in drug waste associated with olaratumab administration to patients with soft tissue sarcoma.

Methods

A retrospective observational study was conducted to describe the weight and BSA data of patients with cancer in EMRs in IMS Oncology (IMS Health, Danbury, CT), a commercial EMR database for capturing detailed, patient-level clinical data in primarily medium and large community-based oncology practices throughout the United States. The EMR weight data for patients with soft tissue sarcoma were then used to evaluate the various options for the second olaratumab vial size and determine the optimal vial volume for minimization of drug wastage.

Study design. Real-world patient weight and BSA data were retrieved from EMRs in the IMS Oncology database. At the time of study execution, the database included information on patients with cancer covering the period January 2000–June 2014, with more robust data available from 2004 on-

ward. The IMS data set included information on more than 840,000 patients with cancer representing a total of 840 facilities in all 50 states. Detailed clinical data available for these patients include but are not limited to cancer diagnosis; cancer stage; TNM Classification of Malignant Tumors notation; patient age, sex, and race; laboratory results and vital-sign data; injectable and oral medications, including chemotherapy and hormonal drugs; dosing; drug regimens; treatment intervals; weight; height; BSA; and body mass index values. Data in IMS Oncology are deidentified in compliance with the Health Insurance Portability and Accountability Act.

The index period for identification of cancer diagnoses was January 2004 through June 2014. The follow-up period for each patient consisted of all patient data collected from the index (i.e., cancer diagnosis) date through the end of the data set in June 2014.

Inclusion criteria. Weight and BSA records were retrieved from the oncology EMR database for patients with soft tissue sarcoma. The weight and BSA records of other patients with cancer were also reviewed, using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes to identify each cancer type as soft tissue sarcoma (171.xx), female breast (174.xx), colorectal (153.xx, 154, 154.0, and 154.1), lung (162.2–162.9), ovarian (183.xx), prostate (185.xx), multiple myeloma (203.0x), or gastric (151.xx) cancer. Per the inclusion criteria, all patients in the study population were 18 years of age or older as of the index date and had at least 2 documented visits to a treating provider (the latter criterion was applied to exclude patients with a "rule-out," or uncertain, diagnosis. Patients' weight and BSA records at the time of the first systemic therapy (order for chemotherapy, biological, or anticancer hormonal agents) were reviewed for patients who had systemic therapy orders during the 30 days prior to the index diagnosis to any time thereafter.

Study endpoints. The key measures were patient weight and BSA at the time of the first dose of systemic anticancer therapy. Compared with BSA records, weight and height data are better populated in the EMR database for the majority of patients and at multiple time points. Therefore, our preference was to calculate each patient's BSA using his or her weight and height records and the method of Du Bois and Du Bois: BSA (m^2) = weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 0.007184$. The height and weight values recorded in closest proximity to the date of the first systemic therapy were used. Only weights recorded within 30 days of the first systemic therapy were included in the analysis; height records recorded in the EMR at any time were included. If either eligible height or eligible weight data were missing, the patient's BSA record was used if the BSA record was available within 30 days of the first systemic therapy. If all of these records were missing, the patient's data were omitted from analyses of BSA; however, the data were retained for other analyses (e.g., analyses of patient demographic characteristics). Other variables of interest included age, race or ethnicity (white, black, Asian, Hispanic, or other), sex, cancer type, stage at diagnosis, and region of residence at the time of diagnosis.

Statistical analysis. Descriptive statistics were used to summarize baseline demographic characteristics (age, race, sex, stage at diagnosis, and region of residence) for the 8 cancer cohorts. The primary descriptive measures of weight and BSA at the time of first systemic therapy (both means ± S.D. values and medians with interquartile ranges) were stratified according to cancer type and sex. Descriptive statistics were generated using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Waste-minimization analysis. The distribution of patient weights in the soft tissue sarcoma population was reviewed. Given the sample size and the division of weight into 1-pound intervals, the resulting histograms of patient weights exhibited considerable "noise." Therefore, the density function in the R program (version 2.15.2, R Core Team, Vienna, Austria) was used to smooth out the noise. Based on visual inspection, the smoothing bandwidth parameter was set to 10 pounds (about 4.5 kg), which produced population densities exhibiting increasing and then decreasing numbers of patients as the weight increased. American patient weights are systematically higher than patient weights in other regions, especially Europe and Asia. To not bias the waste calculation analysis toward heavier patients, who are less likely to be encountered globally, patient weight distributions were truncated at approximately 122 kg. For soft tissue sarcoma, this restriction excluded approximately 4% of patients and lowered the mean patient weight by approximately 1.4 kg.

After the bandwidth parameter was applied and data on patients weighing more than 122 kg were removed, the doses were computed. Olaratumab is being evaluated at a dose of 15 mg/kg and produced as a 10-mg/mL solution. The fractional distribution of weights for the study cohort of patients with soft tissue sarcoma was converted to a population of patients, and for each unique patient weight the dose required was computed. Based on the doses to be delivered, decisions were made regarding the largest and smallest vial sizes to be considered. The analysis constrained the number of vials per administration to a maximum of 6 to minimize or limit needed pharmacy manipulation during sterile compounding and to avoid an excessive number of vials for any given patient. All doses were rounded in increments of 10 mg. All possible vial size combinations were enumerated subject to the constraints described in this section. A C++ program that, for a given distribution of patient weights and a fixed dose per kilogram, computes the population-weighted average waste

Table 1. Cohort Attrition[a]

Criterion	No. Patients Meeting Criterion							
	Soft Tissue Sarcoma	Female Breast Cancer[b]	Colorectal Cancer	Lung Cancer	Ovarian Cancer[b]	Prostate Cancer[b]	Multiple Myeloma	Gastric Cancer
Diagnosis of interest documented in EMR	7,400	206,106	75,297	106,281	15,648	46,582	19,068	8,127
Age ≥ 18 yr at index (diagnosis date)	7,308	205,995	75,246	106,242	15,615	46,535	19,066	8,118
≥ 2 visits to treating provider documented in EMR	6,647	191,472	68,863	97,771	14,438	41,810	18,209	7,464
Documented systemic chemotherapy	2,291	110,534	35,044	56,411	8,020	16,510	10,374	3,866
BSA and height or weight values documented within 30 days of first systemic therapy	2,285	110,210	35,008	56,354	8,005	16,360	10,349	3,853

[a]BSA = body surface area, EMR = electronic medical record.
[b]Attrition shows all patients (male and female). The entire patient sample consisted of 242,424 patients, of whom 177 patients had miscoded cancer diagnoses or sex in the EMR; data on these patients were not included for review in analyses of demographic and clinical characteristics, weight, or BSA.

associated with a given set of vial size combinations was written.

At the time of our study, olaratumab had already been formulated for administration as a 500-mg dose, produced as a 10-mg/mL solution in a 50-mL vial, for use in clinical trials. The manufacturer wanted to ensure that any dose considered was aligned with the manufacturer's current vial platform (vial sizes of 3, 5, 10, 20, and 50 mL). Due to the 6-vial constraint, dosage forms containing less than 10 mL were not considered. Other manufacturing considerations included meeting the minimum fill levels for the respective vial sizes, avoiding the appearance of underfill or overfill, and maintaining a fill volume that was "elegant" (i.e., a whole number rounded to the tens). The aforementioned calculations were performed combining doses with a 500-mg dose, and the waste and other characteristics were estimated from each combination.

Waste calculations are reported here as either a mean amount per patient or as a fraction or percentage of the total dose administered. A patient weighing 80 kg and administered a dose of 15 mg/kg would need 1,200 mg of a given drug. If only a single vial size (500 mg) were available, 3 500-mg doses would be ordered, with 1,200 mg administered to the patient and 300 mg (20% of the ordered dose) wasted.

Results

Patient body weight and BSA. Table 1 displays cohort attrition for each cancer type according to the eligibility criteria. The majority of patients (>99%; 242,424 of 243,050 patients) who received systemic chemotherapy also had eligible weight, height, or BSA records. The entire patient sample consisted of 242,424 patients, of whom 177 had miscoded cancer diagnoses or sex in the EMR (i.e., 146 men had *ICD-9-CM* diagnosis codes for female breast cancer, 10 men had codes for ovarian cancer, and 21 women had codes for prostate cancer). Table 2 shows demographic characteristics and cancer stage at di-

Table 2. Cohort Demographics and Clinical Characteristics

Variable	Soft Tissue Sarcoma (*n* = 2,285)	Female Breast Cancer[a] (*n* = 110,041)	Colorectal Cancer (*n* = 35,008)	Lung Cancer (*n* = 56,354)	Ovarian Cancer[a] (*n* = 7,995)	Prostate Cancer[b] (*n* = 16,335)	Multiple Myeloma (*n* = 10,349)	Gastric Cancer (*n* = 3,853)
Mean ± S.D. age at diagnosis, yr	60 ± 15	60 ± 12	63 ± 12	66 ± 10	63 ± 12	71 ± 8	66 ± 11	63 ± 12
Female, no. (%)	1,095 (47.9)	110,041 (100.0)	16,164 (46.2)	26,296 (46.7)	7,995 (100.0)	. . .[c]	4,627 (44.7)	1,341 (34.8)
Race/ethnicity, no. (%)								
White	1,277 (55.9)	66,277 (60.2)	19,140 (54.7)	31,225 (55.4)	4,561 (57.0)	9,368 (57.3)	5,629 (54.4)	1,663 (43.2)
Black	216 (9.5)	8,540 (7.8)	2,732 (7.8)	3,061 (5.4)	457 (5.7)	1,325 (8.1)	1,229 (11.9)	414 (10.7)
Asian	21 (0.9)	1,231 (1.1)	388 (1.1)	365 (0.6)	85 (1.1)	84 (0.5)	80 (0.8)	120 (3.1)
Hispanic	20 (0.9)	847 (0.8)	264 (0.8)	166 (0.3)	61 (0.8)	109 (0.7)	73 (0.7)	80 (2.1)
Other	136 (6.0)	5,793 (5.3)	1,852 (5.3)	2,294 (4.1)	411 (5.1)	791 (4.8)	732 (7.1)	310 (8.1)
Unknown	615 (26.9)	27,353 (24.9)	10,362 (30.4)	19,243 (34.1)	2,420 (30.3)	4,658 (28.5)	2,606 (25.2)	1,266 (32.9)
U.S. Census region, no. (%)[d]								
Northeast	233 (10.2)	12,076 (11.0)	4,244 (12.1)	6,837 (12.1)	1,013 (12.7)	2,080 (12.7)	1,321 (12.8)	571 (14.8)
Midwest	264 (11.6)	11,817 (10.7)	4,359 (12.5)	7,236 (12.8)	1,177 (14.7)	1,685 (10.3)	1,269 (12.3)	421 (10.9)
South	1,539 (67.4)	74,307 (67.5)	22,160 (63.3)	36,751 (65.2)	4,522 (56.6)	10,411 (63.7)	6,556 (63.3)	2,383 (61.8)
West	238 (10.4)	11,387 (10.4)	4,045 (11.6)	5,305 (9.4)	1,250 (15.6)	2,099 (12.9)	1,165 (11.3)	457 (11.9)
Unknown	11 (0.5)	454 (0.4)	200 (0.6)	225 (0.4)	33 (0.4)	60 (0.4)	38 (0.4)	21 (0.5)
Stage at diagnosis, no. (%)[e]								
0	1 (0.0)	1,496 (1.4)	19 (0.05)	6 (0.01)	2 (0.03)	3 (0.02)	0 (0.0)	1 (0.03)
I	12 (0.5)	25,540 (23.2)	638 (1.8)	2,014 (3.6)	452 (5.7)	140 (0.9)	16 (0.2)	131 (3.4)
II	11 (0.5)	22,469 (20.4)	3,728 (10.6)	1,899 (3.4)	265 (3.3)	1,113 (6.8)	14 (0.1)	338 (8.8)
III	31 (1.4)	8,430 (7.7)	7,919 (22.6)	6,455 (11.5)	1,565 (19.6)	403 (2.5)	13 (0.1)	384 (10.0)
IV	63 (2.8)	6,872 (6.3)	8,030 (22.9)	11,570 (20.5)	1,227 (15.3)	4,180 (25.6)	24 (0.2)	1,048 (27.2)
Unknown[f]	2,167 (94.8)	45,234 (41.1)	14,674 (41.9)	34,410 (61.1)	4,484 (56.1)	10,496 (64.3)	10,282 (99.4)	1,951 (50.6)

[a]Data are for women only (miscoded cases in men excluded from analysis).
[b]Data are for men only (miscoded cases in women excluded from analysis).
[c]Not applicable.
[d]The four regions are based on U.S. Census rules: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania); Midwest (Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota); South (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas); and West (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington).
[e]Stage closest to diagnosis (i.e., within 120 days of index date). In some cases in which cancers were documented as "stage X" or staging data were missing, cancers were recoded as stage IV on the basis of TNM Classification of Malignant Tumors notations.
[f]Includes cases in which staging data were not documented and cases involving notations of "stage X," "limited," "extensive," or "occult."

Table 3. Cohort Data on Body Weight and Body Surface Area[a]

Variable	Soft Tissue Sarcoma (*n* = 2,285)	Female Breast Cancer[b] (*n* = 110,041)	Colorectal Cancer (*n* = 35,008)	Lung Cancer (*n* = 56,354)	Ovarian Cancer[b] (*n* = 7,995)	Prostate Cancer[c] (*n* = 16,335)	Multiple Myeloma (*n* = 10,349)	Gastric Cancer (*n* = 3,853)
Results of Weight Analysis Stratified by Sex								
Male, no.	1,179	. . .[d]	18,524	29,446	. . .	16,061	5,660	2,465
Mean ± S.D. weight, kg	85.27 ± 18.62	. . .	85.69 ± 18.82	81.20 ± 17.33	. . .	86.18 ± 17.84	86.13 ± 17.53	79.31 ± 18.17
Median (IQR) weight, kg	82.55 (72.58–95.53)	. . .	83.46 (72.94–95.71)	79.38 (69.13–91.08)	. . .	83.92 (73.94–96.16)	83.92 (73.94–95.71)	76.66 (67.59–88.72)
Female, no.	1,078	108,505	15,911	25,711	7,925	. . .	4,559	1,321
Mean ± S.D. weight, kg	72.89 ± 19.93	76.31 ± 18.50	71.17 ± 18.71	67.54 ± 16.96	71.87 ± 18.67	. . .	71.74 ± 18.24	65.43 ± 16.82
Median (IQR) weight, kg	68.69 (58.51–84.28)	73.48 (63.05–86.18)	68.04 (57.97–80.92)	64.86 (55.70–76.66)	68.04 (58.51–81.65)	. . .	68.95 (58.97–81.60)	62.60 (53.07–74.53)
Results of BSA Analysis Stratified by Sex								
Male, no.	1,170	. . .	18,391	29,297	. . .	15,541	5,614	2,453
Mean ± S.D. BSA, m^2	2.01 ± 0.22	. . .	2.01 ± 0.22	1.96 ± 0.21	. . .	2.01 ± 0.21	2.01 ± 0.21	1.93 ± 0.22
Median (IQR) BSA, m^2	2.00 (1.86–2.14)	. . .	2.00 (1.86–2.14)	1.95 (1.82–2.09)	. . .	2.00 (1.86–2.14)	2.00 (1.87–2.14)	1.92 (1.79–2.06)
Female, no.	1,073	107,237	15,797	25,528	7,873	. . .	4,512	1,315
Mean ± S.D. BSA, m^2	1.76 ± 0.22	1.80 ± 0.20	1.74 ± 0.21	1.70 ± 0.20	1.75 ± 0.21	. . .	1.74 ± 0.21	1.67 ± 0.20
Median (IQR) BSA, m^2	1.73 (1.61–1.90)	1.78 (1.66–1.93)	1.72 (1.59–1.87)	1.69 (1.56–1.82)	1.73 (1.60–1.88)	. . .	1.73 (1.59–1.87)	1.65 (1.52–1.80)

[a]IQR = interquartile range, BSA = body surface area.
[b]Data are for women only (miscoded cases in men excluded from analysis).
[c]Data are for men only (miscoded cases in women excluded from analysis).
[d]Not applicable.

agnosis for the cohorts. The mean age of patients in the soft tissue sarcoma cohort was 60 years; the mean ages ranged from 60 to 71 years across the other cancer cohorts. While the majority of patients whose race or ethnicity was documented in the EMR were white, race or ethnicity was not recorded for 25–34% of patients. The study cohorts were disproportionately (57–68%) composed of patients residing in the South versus other U.S. Census regions. Depending on the cohort, stage at diagnosis was unknown in 41–99% of patients.

Table 3 shows weight and BSA for patients at the time of systemic therapy, stratified by cancer type and sex. There were distinct differences across cancer types; patient weights and BSA values were, on average, lower in the lung cancer and gastric cancer cohorts and higher in the female breast cancer cohort relative to cohorts with other cancer types. Across all cancer types, as expected, men tended to have higher weight and BSA values than females. Within each cancer type and sex, the mean and median weight values were largely similar, although the means tended to be slightly higher than the medians because of extreme weight and BSA values in some patients. Across all cancers and for both sexes, patients were consistently heavier in the Midwest than in other U.S. Census regions (data not shown). Patient weights were also consistently higher in patients younger than 65 years compared with those 65 or older (data not shown).

Waste calculation. By applying the analytic methods to the weight data from the 2,285 patients with soft tissue sarcoma, the estimated average waste associated with dispensing of olaratumab to a population of patients with soft tissue sarcoma, assuming the use of only 500-mg/50-mL vials, was approximately 234 mg per patient per administration.

Table 4 shows the waste calculation results for hypothetical scenarios for the use of various potential vial sizes in combination with the existing

500-mg vial. In terms of waste avoidance, the optimal dosage form was 210 mg/21 mL, which yielded a population average waste of 28.68 mg; however, due to the previously described vial size constraints, this was not selected as an appropriate alternative vial size. Instead, it was determined that the best feasible combination was a 10-mg/mL solution (190 mg/19 mL) delivered in a 20-mL vial; we calculated that the use of that vial size in combination with the existing 500-mg/50-mL vials would result in a population-weighted average waste value of just 29 mg per patient per administration, an 87.6% reduction in waste relative to use of 500-mg vials exclusively.

Assuming use of a combination of 190- and 500-mg vials, it was calculated that drug wastage would occur in 65% of olaratumab administrations (Table 4), while 35% of administrations would result in no or negligible waste. We determined that the worst-case scenario of waste generation would occur in a patient weighing 51.3 kg. Dosed at 15 mg/kg, that patient would need 770 mg of olaratumab; the best combination of 190- and 500-mg doses (2 doses of 190 mg and 1 dose of 500 mg, for a total dose of 880 mg) would generate waste of 110 mg. Similar waste generation would result from administration of a dose of 580 mg to a patient weighing 38.7 kg. However, these worst-case scenarios must be placed into context by considering the entire population. Table 4 shows a population-weighted average waste of 29 mg per patient per administration, and we expect that over the long term waste at individual treatment centers will approach the average.

Figure 1 illustrates the combined picture of the real-world weight data from the soft tissue sarcoma population with the 190- and 500-mg olaratumab vials and also demonstrates how combinations of 190- and 500-mg vials can cover the anticipated dose range of olaratumab at 15 mg/kg and displays those doses that can be covered exactly.

Discussion

Reduction of drug waste offers the potential to reduce drug expenditures within a relatively short period without negatively affecting quality of care or limiting specific drug use.[6] Manufacturers can contribute to the reduction of drug waste through the production of multiple appropriate vial sizes for parenteral drugs. However, the selection of appropriate vial sizes depends greatly on the weight and BSA distributions of the targeted cancer patient populations. In this study, we demonstrated how real-world data on patient weight was used to determine the optimal second vial size for olaratumab, which was granted FDA approval in October 2016 for use in patients with soft tissue sarcoma.

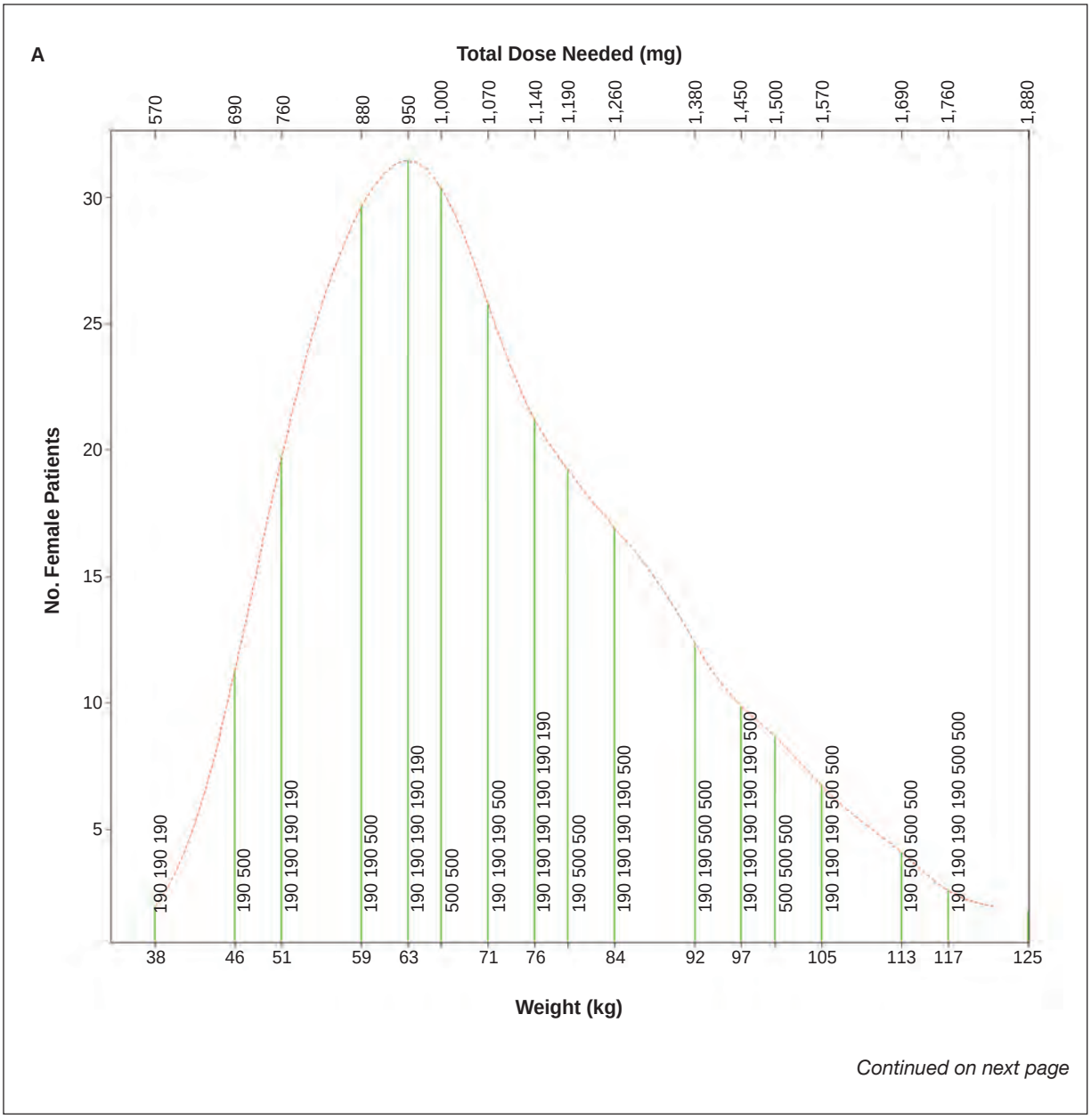
In many instances, manufacturers do not have a financial incentive to proactively produce smaller vial sizes for the commercial market after a product launch. Mindful of the potential impact of drug waste on pharmacy budgets, an opportunity to significantly reduce wastage for a clinically promising investigational agent was explored through the introduction of an additional vial size. Our analyses indicated that the addition of a 190-mg vial size would reduce the population average waste per patient per administration by 87.6%, to just 29 mg.

The waste calculation analyses presented here included a number of considerations and constraints. For example, an important constraint was the need to minimize the number of vials that would have to be manipulated per olaratumab administration. The objectives of waste minimization and vial minimization cannot be simultaneously optimized. At the extreme, producing very small vial sizes would allow for almost any dose with minimal waste. However, preparation would become unduly burdensome for the pharmacy to handle numerous vials. In addition, producing very small vial sizes may increase the potential for medication errors and microbial contamination.[17] Therefore, to control pharmacy handling, we imposed

Table 4. Estimates of Drug Waste and Waste Reduction With Various Olaratumab Vial Sizes

Outcome	Potential Vial Size							
	210 mg	190 mg	140 mg	220 mg	150 mg	90 mg	110 mg	180 mg
Population average waste per patient per administration (mg)	28.68	29.02	30.29	31.61	33.71	35.98	36.25	37.65
Mean no. vials needed	3.89	4.19	4.14	4.17	4.64	4.24	4.31	3.66
% Cases involving waste	60.66	64.72	65.59	65.54	66.50	69.69	68.91	65.82
% Waste reduction relative to use of 500-mg vial only	87.74	87.60	87.06	86.49	85.59	84.63	84.51	83.91

Figure 1. Results of modeling of olaratumab dosing requirements and combinations of 190- and 500-mg vials needed to treat a real-world population of patients with soft tissue sarcoma in relation to various weight values (green lines) and weight distribution (dotted red line) in adult female (panel A) and male (panel B) patients with soft tissue sarcoma.

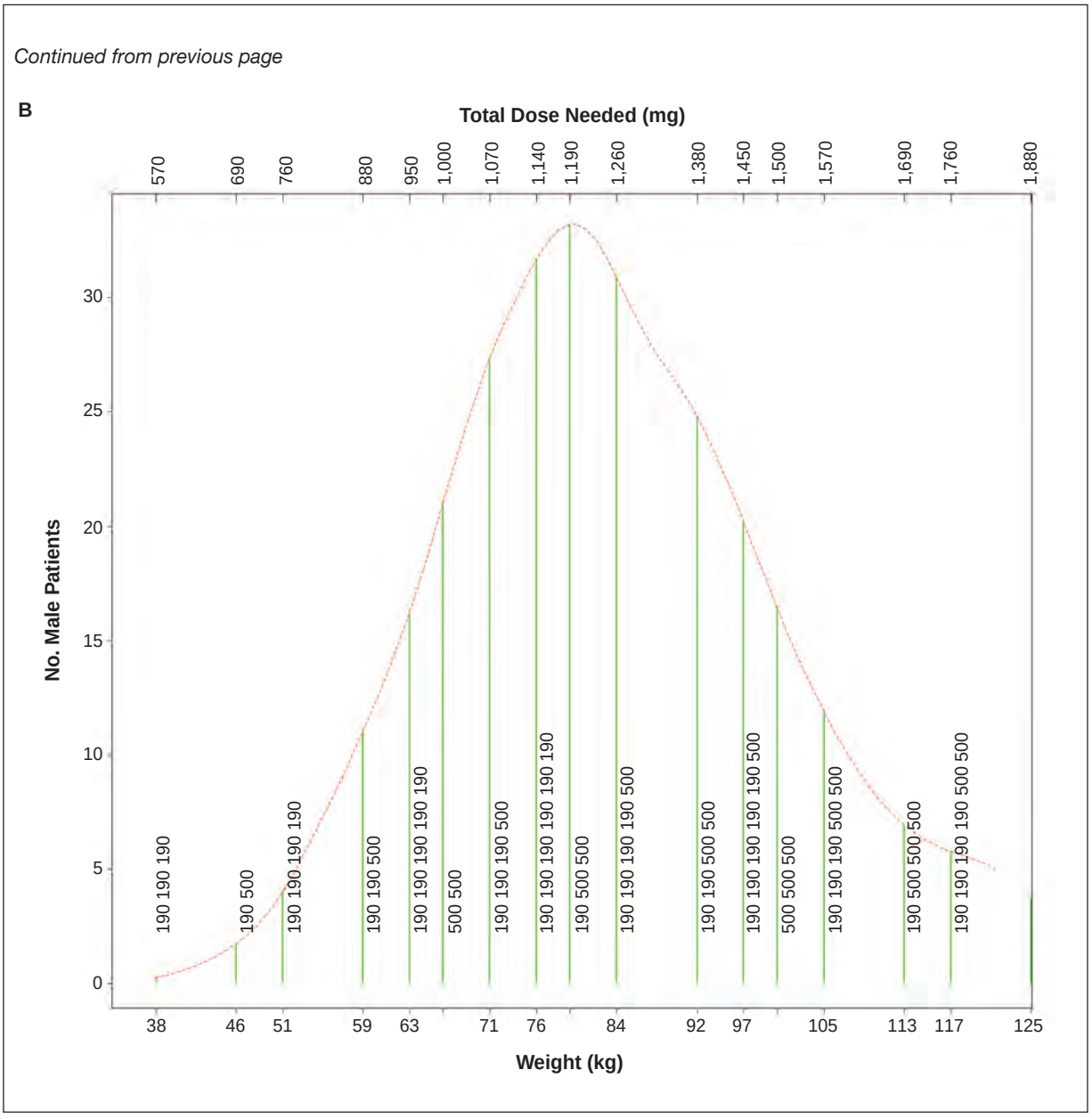


Continued on next page

a limit of no more than 6 vials to be opened for any given patient. Another consideration involved the inclusion and evaluation of atypical vial sizes. In our waste calculations, we found that combinations of vial volumes that are not multiples of each other produce less waste because their use can accommodate a greater variety of doses and offers inherent advantages with regard to applications in other populations (e.g., non-U.S. patients). The ability to accommodate a greater variety of doses is particularly important given the differences in the distributions of body weight and height across regions of the world. In the case of olaratumab administration at a dose of 15 mg/kg, doses of 880, 950, 1,000, 1,070, 1,140, 1,190, and 1,260 mg can all be achieved with 6 or fewer vials containing 500 mg/50 mL or 190 mg/19 mL, whereas with vials containing 500 mg/50 mL and 200 mg/20 mL,

Figure 1. *Continued.*

Continued from previous page



only doses in milligram quantities that are multiples of 100 could be prepared without wastage. In fact, the combination of a 500-mg/50 mL vial and a 190-mg/19 mL vial reduced wastage by 22% compared with a combination of a 500-mg/50 mL vial and a 100-mg/10 mL vial. Finally, it was important to consider assumptions about dose rounding. Dose rounding to the nearest 5–10% has been reported as a frequent and viable waste mitigation strategy by cancer care facilities and providers.[6,9,14,15,18-20] In sensitivity analyses, we assumed dose rounding of 1–5% and found minimal differences in mean population waste and mean number of vials required. Drug waste-minimization calculations must factor in real-world pharmacy and manufacturing contexts in order to be useful for decision-making.

A strength of the study was the use of the entire weight distribution

of 2,285 patients with soft tissue sarcoma rather than reliance on mean or median weight values. This approach accounted for the considerable variability in weight, dosing, and potential waste across the patient population.

Another important strength of the study was the use of real-world patient data versus clinical trial patient data. In the Phase II study of olaratumab for soft tissue sarcoma,[16] several patients with large weight values caused the overall population (n = 178 patients) weight distribution to be heavier than the real-world patient weights from the IMS Oncology EMR database. Hence, having a larger sample size of representative patients is an important consideration for the waste calculations from a payer perspective.

In addition to using real-world data to optimize vial sizes, with this study we aimed to provide healthcare providers, health technology assessors, payers, and manufacturers with population-based estimates of weight and BSA for U.S. patients with cancer. The use of BSA- and weight-based dosing is relevant to health technology assessment (HTA) agencies, healthcare systems, and payers that need to estimate the average yearly cost of a particular anticancer agent for their patient populations.[13] Cost-effectiveness analyses and budget impact models rely on accurate assessments of BSA or weight to estimate mean dose per administration of i.v. drug per patient[13] and associated costs, and increasingly, these models attempt to model or account for waste. According to a recent systematic review, drug wastage was considered in the primary, or base-case, analysis of parenteral therapies for hematologic malignancies in 2 of the 3 HTA reports reviewed, and consideration of wastage in the model changed the calculated incremental cost-effectiveness ratio.[21]

There is no standard BSA or weight on which to base dosing and estimate the number of vials needed (and costs) for each drug administration.[13] As a result, varying BSA values have been used by manufacturers and evidence review groups in the evaluation of new agents. Even small differences in dose estimates could have a significant impact on cost projections when accounting for partial use of additional vials and the associated drug wastage. The weight and BSA values and distributions used in dosage calculations can have important consequences for pharmacy budgets and reimbursement decisions. However, a literature search revealed that only 2 pertinent studies (using data from real-world clinical practice in the United Kingdom) have been conducted within the last 10 years.[13,22] The patients in our U.S. cancer cohorts had somewhat greater weight and BSA values than patients in the U.K. cancer cohorts, although neither of these studies assessed weight in patients with soft tissue sarcoma.

Our study had several limitations. In the absence of robust histology data, cases of soft tissue sarcoma are difficult to identify using real-world data. We identified patients with soft tissue sarcoma in the EMR data by searching for an *ICD-9-CM* diagnosis code of 171.xx, which will not identify sarcomas occurring in organs or other tissues that are classified under other, tumor location–specific codes. Also, weight loss is a common occurrence during the course of systemic therapy, but our waste calculations captured only weight at initiation of systemic therapy rather than weight changes over time. In addition, we did not distinguish between neoadjuvant, adjuvant, and palliative systemic therapies. However, a prior study found no differences in mean BSA results among patients receiving those forms of therapy, even though the palliative chemotherapy included second- and later-line regimens.[13] Moreover, our study included a large sample, but patients from the South were overrepresented in the EMR data set (they constituted approximately 67% of the soft tissue sarcoma cohort); therefore, our cohorts may not be representative of the U.S. cancer population as a whole. Finally, the formula of DuBois and DuBois was used to calculate BSA, although some pharmacies may use the Mosteller formula; however, no practical differences in the resulting waste-minimization calculations would be expected.

Two objectives were achieved in this study. First, the study provided estimates for weight and BSA for a large sample of men and women with cancer receiving systemic therapy in U.S. outpatient oncology clinics. These real-world patient weight and BSA estimates are important inputs for calculating the cost impact or cost-effectiveness of new cancer therapies in pharmacy budget projections, HTA initiatives, and budget impact models. In addition, the olaratumab study demonstrated how real-world patient weight estimates may be used during drug development and manufacturing to optimize drug vial sizes and reduce drug waste. Based on the weight distribution of patients with soft tissue sarcoma, it was determined that adding a 190-mg vial to the existing product line would reduce anticipated olaratumab waste by 87%; this vial size is now available in the United States. The study demonstrated how optimizing vial sizes is inseparably linked to knowing the population weight and BSA distribution; the choice should not be made in isolation from real-world data if such data are available. The olaratumab study also shows how a seemingly minor change to drug vial sizes can have a significant populationwide impact on drug waste. Using real-world data, manufacturers may implement practices to select vial sizes that will significantly reduce drug waste.

Conclusion

Analysis of real-world patient weight and BSA data allowed olaratumab vial size optimization to enable maximal dosing flexibility with minimal drug waste.

Acknowledgments

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the vial size project and review of the manuscript, David R. Nelson, M.S., for providing meaningful data and data quality reviews, Diane E. Michael, M.A., for data analysis support, Teri Tucker, B.A., for editing the manuscript, and Jeanne Claypoole, B.A., for performing a writing quality review.

Disclosures

Dr. Sheffield, Ms. Beyrer, Dr. Watson, Ms. Stafford, and Mr. Mills are employees of Eli Lilly and Company and own stock in the company. Dr. Ale-Ali participated on Eli Lilly and Company advisory boards during the study and is currently an employee of the company. The authors have declared no other potential conflicts of interest.

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Exhibit C

The New York Times | http://nyti.ms/1UvzN9h

HEALTH

Waste in Cancer Drugs Costs $3 Billion a Year, a Study Says

By GARDINER HARRIS MARCH 1, 2016

WASHINGTON — The federal Medicare program and private health insurers waste nearly $3 billion every year buying cancer medicines that are thrown out because many drug makers distribute the drugs only in vials that hold too much for most patients, a group of cancer researchers has found.

The expensive drugs are usually injected by nurses working in doctors' offices and hospitals who carefully measure the amount needed for a particular patient and then, because of safety concerns, discard the rest.

If drug makers distributed vials containing smaller quantities, nurses could pick the right volume for a patient and minimize waste. Instead, many drug makers exclusively sell one-size-fits-all vials, ensuring that many smaller patients pay thousands of dollars for medicine they are never given, according to researchers at Memorial Sloan Kettering Cancer Center, who published a study on Tuesday in BMJ, formerly known as the British Medical Journal.

Some of these medicines are distributed in smaller vial sizes in Europe, where governments play a more active role than the United States does in drug pricing and distribution.

"Drug companies are quietly making billions forcing little old ladies to buy

enough medicine to treat football players, and regulators have completely missed it," said Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering and a co-author of the study. "If we're ever going to start saving money in health care, this is an obvious place to cut."

The researchers analyzed the waste generated by the top 20 selling cancer medicines and concluded that insurers paid drug makers $1.8 billion annually on discarded quantities and then spent about $1 billion on markups to doctors and hospitals.

Some non-cancer drugs also generate considerable waste, including Remicade, an arthritis drug sold by Johnson & Johnson for which an estimated $500 million of the drug's $4.3 billion in annual sales comes from quantities that are thrown away, researchers found. But such non-cancer drugs were not included in the study's estimates of total waste.

In one example, the study said that in the United States Takeda Pharmaceuticals sells Velcade, a drug for the treatment of multiple myeloma and lymphoma, only in 3.5-milligram vials that sell for $1,034 and hold enough medicine to treat a person who is 6 feet 6 inches tall and who weighs 250 pounds. If a patient is smaller, then a quantity of the precious powder is thrown away.

Lena Haddad, 53, of Germantown, Md., who has been living with multiple myeloma for four years, now gets a weekly dose of 1.8 milligrams of Velcade. On a recent day at Ms. Haddad's doctor's office in Bethesda, Md., a nurse, Patricia Traylor, took a vial of Velcade from a large drug cabinet. She injected a syringeful of saline into the vial and shook it, pushed a needle into the vial and withdrew about half the contents. Then she threw out the vial with the remaining medicine.

"You can't use the remainder for the patient the next time she comes in or use it on another patient, so it has to be discarded as waste," Ms. Traylor said.

Safety standards permit nurses to use drug leftovers in other patients only if used within six hours and only in specialized pharmacies.

Told that she was using only about half of the drug that was purchased, Ms. Haddad said she was shocked.

“No wonder my premiums keep going up,” she said.

Medicare and many private insurers charge patients drug co-payments of as much as 20 percent, which can add up to tens of thousands of dollars annually for the latest drugs; much is spent on cancer medicines that patients never receive, according to the study.

Dr. Dixie-Lee Esseltine, vice president for oncology clinical research at Takeda, wrote in an email that the pharmaceutical firm “worked closely with the F.D.A. to establish the Velcade vial size of 3.5 mg to ensure that one vial of Velcade would provide an adequate amount of the drug for a patient of almost any size.”

Velcade is sold in Britain in both 1-milligram and 3.5-milligram vials.

Takeda is expected to earn $309 million this year on supplies of Velcade that are discarded, an amount that represents 30 percent of the drug’s overall sales in the United States, the cancer researchers estimated. If Takeda provided an additional vial size of 0.25 milligram, waste would be slashed by 84 percent, also reducing Velcade’s sales in the United States by $261 million annually, the researchers calculated.

“You have these incredibly expensive drugs, and you can only buy them in bulk,” said Dr. Leonard Saltz, who leads the pharmacy and therapeutics committee at Memorial Sloan Kettering and was a co-author of the study. “What’s really interesting is they’re selling these drugs in smaller vials in Europe, where regulators are clearly paying attention to this issue.”

Christopher Kelly, a spokesman for the Food and Drug Administration,

said the agency objected to companies' proposed vial sizes only if it believed that an excessively large volume of medicine "could lead to medication errors or safety issues due to inappropriate multiple dosing."

In other words, as long as nurses are not tempted to do anything but discard additional quantities, the drug agency is fine with extra-large, one-size-fits-all packaging. Congress has not given the drug agency the authority to consider cost in its decisions.

"Companies propose the vial sizes that they would like to market," Mr. Kelly said.

Rising drug prices have been a concern for many years, and high initial prices and subsequent increases are an industrywide phenomenon. The last 10 cancer drugs approved before July 2015 have an average annual price of $190,217, and major drug makers routinely increase the prices of big sellers 10 percent or more each year, far above the rate of inflation.

The industry explains that high prices are needed to fund research, but companies such as Pfizer and Merck spend just 17 percent of their revenues finding new drugs, according to their financial statements. Far more goes to marketing and profits.

For decades, cancer doctors largely ignored the issue of pricing, but as their patients became impoverished, some began to speak up. In 2012, Dr. Bach and Dr. Saltz wrote an Op-Ed article in The New York Times announcing that their hospital would not purchase a new cancer drug that was twice as expensive as but no more effective than an existing medicine. The maker of the drug slashed its price.

Dr. Bach and Dr. Saltz say they have since become concerned that prices of new cancer medicines have almost no connection with their lifesaving potential. Dr. Bach recently unveiled a complex calculator of drug value.

But there was nothing complex about measuring the value of a drug that was thrown away, Dr. Saltz said, since the value to the patient was zero.

The two doctors have proposed that the government either mandate that drug makers provide medicines in enough vial sizes to minimize waste, or mandate that drug makers refund the government for wasted quantities.

Dr. Saltz first noticed the problem of waste when he was considering adding Keytruda, a new drug for metastatic lung cancer and melanoma, to the hospital's list of drugs to be used on patients. Although a 150-pound patient would need 136 milligrams of the drug, Dr. Saltz noticed that Merck, its manufacturer, sold the medicine only in 50-milligram vials — ensuring waste.

"I thought that was really cynical," Dr. Saltz said in an interview. "And then it got worse."

In February 2015, Merck introduced 100-milligram vials and stopped selling Keytruda in 50-milligram vials, ensuring far larger amounts of waste. The company still sells 50-milligram vials of the drug in Europe.

Pamela L. Eisele, a Merck spokeswoman, said the company hoped to persuade the F.D.A. to approve a fixed dose of 200 milligrams of Keytruda for all patients, higher than the dose presently given to nearly all patients. In studies given to the drug agency, there was no evidence that the higher dose was more effective, Ms. Eisele said, but the fixed dose "will eliminate wastage."

Since the extra medicine does nothing to help patients, Dr. Bach said that the company was advocating that waste be injected into patients rather than thrown away.

Under its present dosing, Merck would earn $2.4 billion over the next five years from discarded quantities of Keytruda, half of which would result from switching to 100-milligram vials, the researchers estimated.

Some cancer drugs have little waste.

Treanda, which is used to treat leukemia and non-Hodgkin's lymphoma and is manufactured by Teva Pharmaceuticals, is packaged in four separate dosages so only 1 percent of the drug is wasted, on average.

But 18 of the top 20 cancer medicines are sold in just one or two vial sizes, so on average 10 percent of the volume of cancer drugs purchased by doctors and hospitals is discarded, the researchers say.

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A version of this article appears in print on March 1, 2016, on page B1 of the New York edition with the headline: Researchers Describe Costly Waste in Cancer Drugs.

Exhibit D

The Washington Post

To Your Health

Americans are wasting $3 billion a year on discarded cancer drugs

By Laurie McGinley March 1

Almost $3 billion a year in expensive cancer drugs are wasted because their single-use packages contain more medication than is needed -- and the leftover drug is thrown away for safety reasons, according to a new analysis by researchers.

The study focused on 20 cancer drugs that are infused -- administered intravenously or injected -- by doctors' offices or hospitals. These come in dosages based on patients' weights and body sizes, but often the doses are too large and the remainder is tossed out, the analysis found.

"It's literally paying for drugs that go in the trash," said Peter Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center in New York. Bach co-authored the study, which was published Tuesday in BMJ, formerly known as British Medical Journal. To increase profits, pharmaceutical companies "are finding a way to charge patients and insurers for drugs that they don't even take," he said.

The study concluded that Medicare and private insurers, as well as patients, pay companies about $1.8 billion a year for medications that are thrown away. They pay another $1 billion to doctors and hospitals as price markups on those discarded medications, according to the study. The analysis was conducted against the backdrop of rapidly rising price increases in both new and older cancer drugs.

"This study reveals that billions of dollars are wasted on expensive cancer drugs, due to the way they are packaged in single doses. This practice greatly inflates profits but is waste that we can no longer afford," John Rother, president and chief executive of the National Coalition on Health Care, said in an email.

But Allyson Funk, senior director of communications at the trade group Pharmaceutical Research and Manufacturers of America noted in a statement that developing and manufacturing cancer medications remains extremely complex and subject to strict regulation by the Food and Drug Administration.

"Decisions regarding vial size are tied to a product's initially approved dosage and labeled use, taking into account that different patients will have different needs," she said. "Vial fill size must be approved by FDA as part of the sponsor's drug application and any excess volume must meet FDA standards outlined in regulations." Any change in vial sizes requires FDA approval, which can take months, she said.

The FDA, which regulates the safety and effectiveness of drugs, doesn't have authority to weigh cost in considering medications, and Bach said he didn't think the agency could order drug companies to use certain vial sizes. But he said he thinks it could, and should, encourage the companies to sell their products in various vial sizes to minimize leftover medication.

An FDA statement noted that officials had not yet reviewed the article but that the agency "works with firms to make sure the proposed vial size is appropriate for the intended use of the product, especially where there are safety concerns about medication errors or the potential that excess drug could be used inappropriately to treat multiple patients from the same vial (which raises concerns about cross-contamination)."

The researchers who did the analysis also said government agencies should develop a consistent policy on whether a vial can be used on more than one patient. Though the Centers on Medicare and Medicaid Services encourages such "vial sharing," they said, the Centers for Disease Control and Prevention considers it unsafe.

Read more:

Scientists think anti-oxidants may boost cancer, not restrain it.

Tapeworms can transmit cancer cells to humans: CDC

Exhibit E

U.S. FOOD & DRUG ADMINISTRATION

June 8, 2017

Request Number: 2017-4747

Richard Cornfeld
1010 Market St, Suite 1720
St. Louis, MO 63101

Subject of Request: Records related to the vial size of 190mg/19ml for Lartruvo

Dear Sir/Madam:

The Food and Drug Administration (FDA) has completed processing your request for records under the Freedom of Information Act (FOIA). I apologize for any delay in responding to you.

We are denying your entire request. The estimated volume of the records we are denying is information from a pending product supplement. Documents relating to a pending application are not releasable. Once the supplement is approved you may submit a new request to receive those records.

The following exemption(s) of FOIA, 5 U.S.C. 552, are the authority for denying you access to the non-disclosable material: (b)(4) Trade secret and confidential commercial information. We have included citations to the FOIA and FDA's regulations for your information.

Section 5.31(d) of the implementing regulations of the Department of Health and Human Services (DHHS) are applicable to this denial. The regulations are contained in the Code of Federal Regulations (CFR), Title 45.

The following sections of the implementing regulations of FDA and reasons applicable to this denial contained in the Code of Federal Regulations (CFR), Title 21 are

- 20.61(b)(c), 601.51(d)(1) Trade secret and confidential commercial information, in general, and information, not previously publicly disclosed, in a pending Biological License Application (BLA).

FDA's Regulations at CFR Part 20 are available at:
http:www.access.gpo.gov/nara/cfr/waisidx_04/21cfr20_04.html

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision. Your appeal must be mailed within 90 days from the date of this response, to: Ms. Catherine Teti, Deputy Agency Chief FOIA Officer, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Public Affairs, Room 729H, 200 Independence Avenue, S.W., Washington, DC 20201. Please clearly mark both the envelope and your letter "FDA Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute

U.S. Food and Drug Administration
5630 Fishers Lane, Room 1035
Rockville, MD 20857
www.fda.gov

without going through the appeals process, please contact **Katherine Uhl at 301-796-8975**. You may also contact the FDA FOIA Public Liaison for assistance at: Office of the Executive Secretariat, US Food & Drug Administration, 5630 Fishers Lane, Room 1050, Rockville, MD 20857, E-mail: FDAFOIA@fda.hhs.gov.

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is as follows: Office of Government Information Services, National Archives and Records Administration, 8601 Adelphi Road–OGIS, College Park, MD 20740-6001; telephone at 202-741-5770; toll free at 1-877-684-6448; or facsimile at 202-741-5769; e-mail at ogis@nara.gov.

If you have any questions, please contact Katherine Uhl at 301-796-8975.

Sincerely yours,

Sarah B. Kotler -A

Digitally signed by Sarah B. Kotler -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130022 4183, cn=Sarah B. Kotler -A
Date: 2017.06.08 08:11:30 -04'00'

Sarah Kotler
Director
Division of Freedom of Information